Dalbavancin for the Treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

United States Food and Drug Administration

Anti-infective Drugs Advisory Committee

March 31, 2014

DURATA THERAPEUTICS®

Meeting Agenda

Introduction	**Michael Dunne, MD** Chief Medical Officer Durata Therapeutics, Inc.
Clinical Efficacy	
Clinical Safety	**Sailaja Puttagunta, MD** Executive Director Durata Therapeutics, Inc.

Consultants

Beth Goldstein, PhD	**Microbiology** **Independent Consultant**
Paul Ambrose, PharmD	**Clinical Pharmacology** **Institute for Clinical Pharmacodynamics**
Anita Das, PhD	**Statistics** **Senior Vice President, InClin, Inc.**

Introduction

Michael Dunne, MD

Chief Medical Officer
Durata Therapeutics, Inc.

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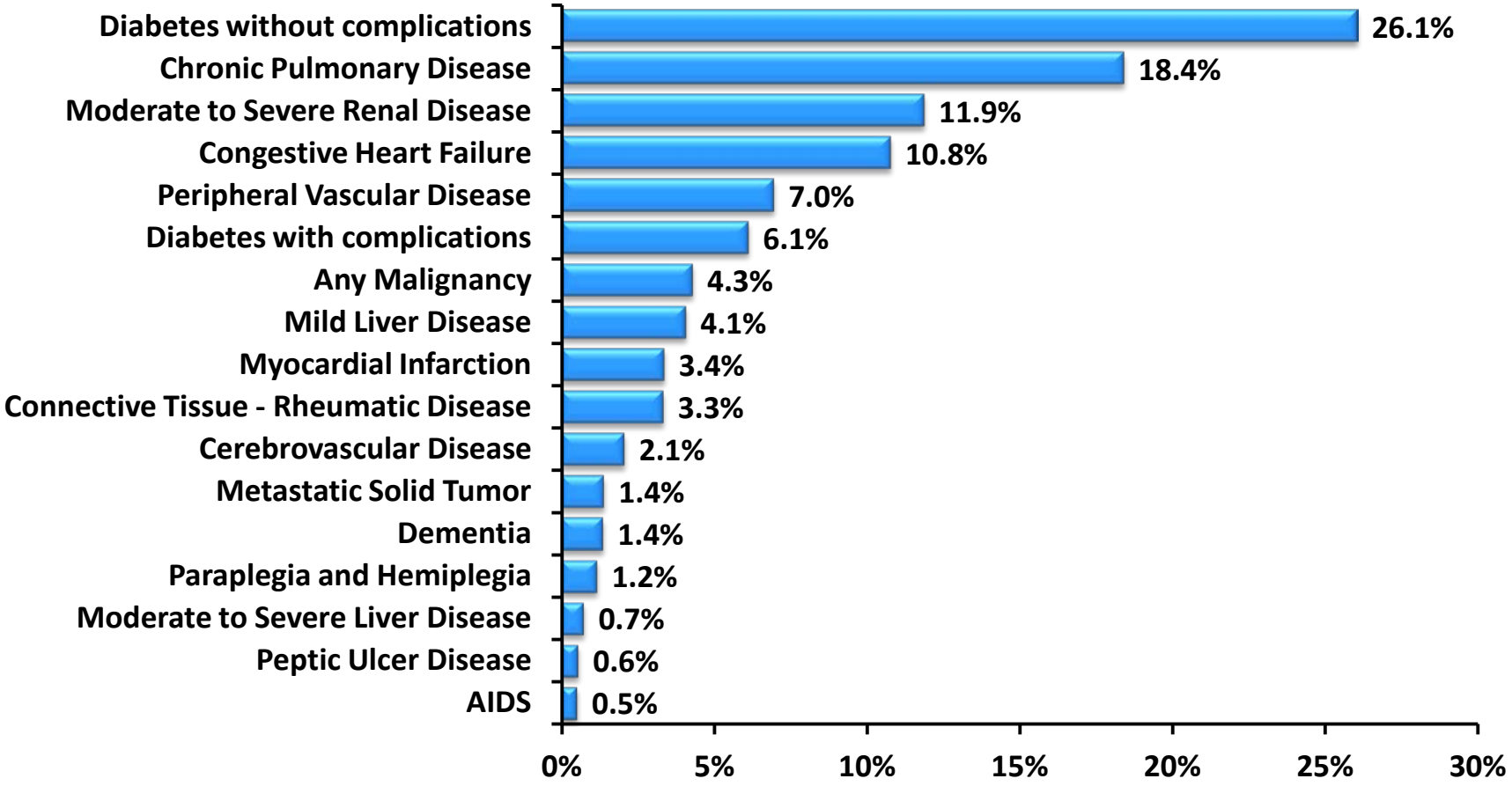
The Incidence of Skin and Skin Structure Infections is Increasing

- Emergency department visits increasing
  - From 1 million to 3.5 million visits (1993-2005)
  - From 1.4% to 3.0% of all ED cases
- 14% of patients seen in the ED require hospitalization
  - Admitted from 4.7 (cellulitis) to 7.2 days (traumatic wounds)
- Among hospitalized patients:
  - Disease severity: mild (30%), moderate (43%), major (23%)
  - Mortality rates of 1% to 4%
  - 50% of patients require structured continuing care at discharge

Healthcare Cost and Utilization Project National Inpatient Sample. (HCUP-NIS) for Acute Bacterial Skin and Skin Structure Infections (ABSSSI). Pallin et al. Ann Emer Med.2008;51:291-298

Comorbidities Associated With ABSSSI Are Common

Most prevalent comorbidities: Diabetes mellitus, COPD, Renal disease and CHF



Healthcare Cost and Utilization Project National Inpatient Sample.
(HCUP-NIS) for Acute Bacterial Skin and Skin Structure Infections (ABSSSI; sample year 2011).

Serious Skin Infections Treatment Options

- Treatment for serious infections is empiric
  - Culture results take 2 to 5 days
  - Need coverage of *S. aureus,* including MRSA, and streptococci
- IV therapy is preferred
  - Concerns with oral therapy center on adherence with subsequent doses and reduced absorption in patients with impaired GI bloodflow

IDSA Recommended MRSA Antibiotics	Dose
Vancomycin[a]	30 mg/kg/day IV, divided doses
Linezolid[a]	600 mg IV/oral, twice a day
Clindamycin[a]	600 mg/kg IV, or 450 mg oral, every 8 hours
Daptomycin[a]	4 mg/kg IV, every 24 hours
Doxycycline, Minocycline	100 mg oral, twice daily
Trimethoprim-Sulfa	1-2 double-strength tablets, oral, twice daily
Televancin[a]	10 mg/kg IV, once daily

2005 IDSA recommendation for MRSA. [a] 2011 IDSA recommendation for complicated skin infections.

Limitations of Approved Treatment Options

Issues with existing options include:

- **Existing IV therapies**
  - Daily dosing limits potential for outpatient treatment
- **Vancomycin**
  - Efficacy concerns at higher MIC;
  - Dose limiting toxicities require drug monitoring
- **Daptomycin**
  - Development of resistance on therapy;
  - Rhabdomyolysis;
  - Toxicity with aminoglycosides
- **Linezolid**
  - Mitochondrial toxicity effects the bone marrow causing cytopenias and limits the duration of treatment;
  - Serotonin syndrome liability impacts potential patient population

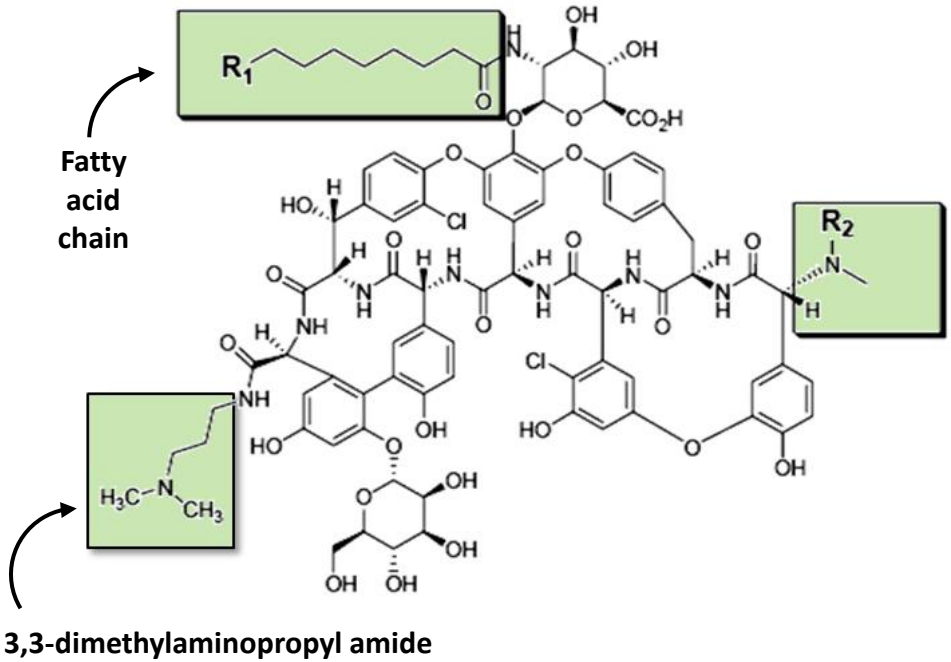
Dalbavancin Proposed Indication

DALVANCE™ (dalbavancin HCl) for injection is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible strains of the following gram-positive microorganisms:

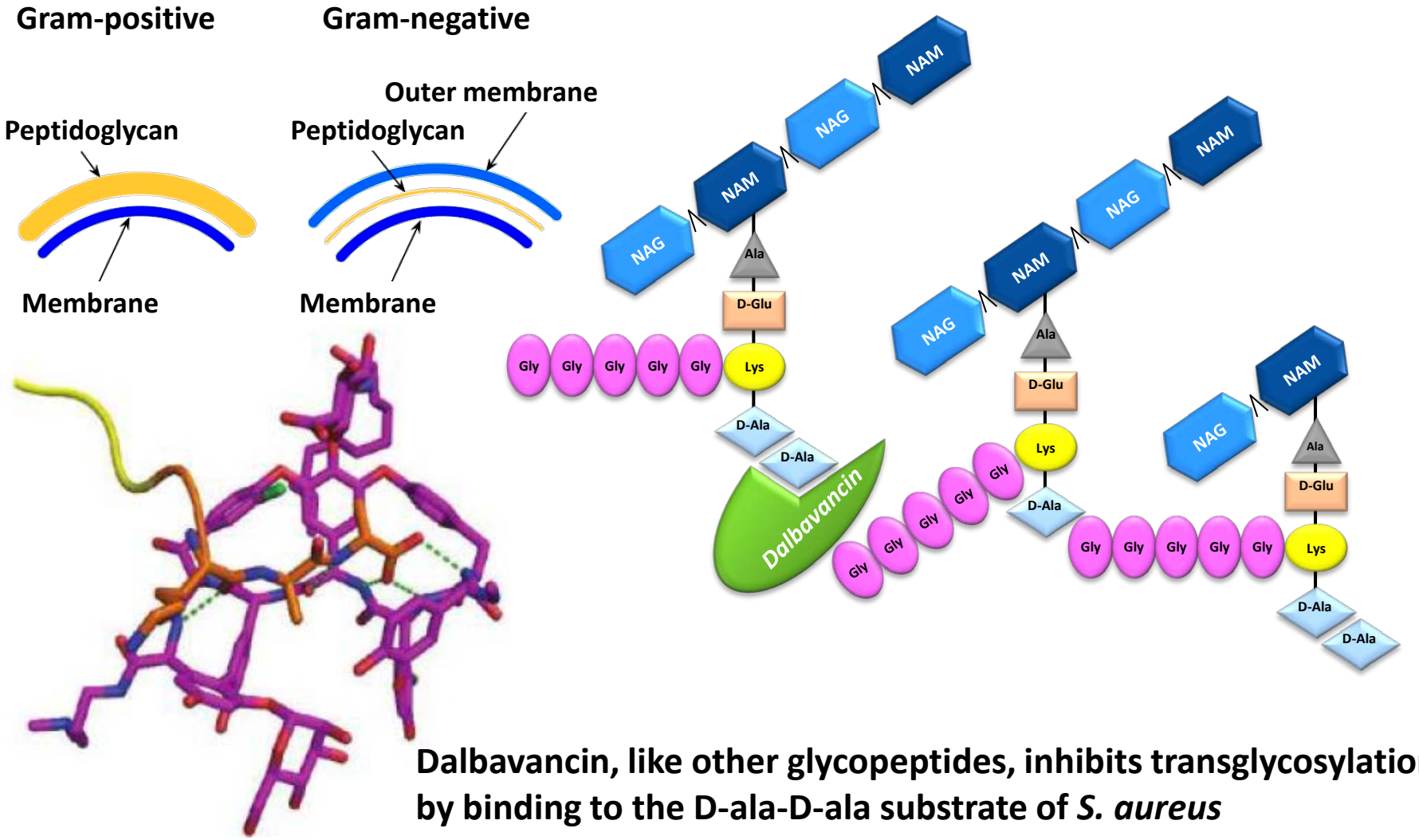
- *Staphylococcus aureus*
  - including methicillin-susceptible and methicillin-resistant strains
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*)

Structure of Dalbavancin

- Long fatty acid chain correlates with extended half life ($t_{1/2}$) in vivo
- 3,3-dimethylaminopropyl amide substituent enhances antibacterial activity of dalbavancin
- R2 substitutions define family of homologues, all with antibacterial activity



Dalbavancin Mechanism of Action



Dalbavancin, like other glycopeptides, inhibits transglycosylation by binding to the D-ala-D-ala substrate of *S. aureus*

Summary of Dalbavancin Microbiology Results

Summary of nine-year (2002-2010) surveillance of dalbavancin potency against 7 organism groups

	MIC, µg/mL			% at MIC, µg/mL		
Organism (No. tested)	**50%**	**90%**	**Range**	**≤0.25**	**≤0.5**	**≤1**
S. aureus (60,159)	0.06	0.06	≤0.03-0.5	>99.9	100.0	100.0
Methicillin resistant (MRSA)	0.06	0.06	≤0.03-0.5	>99.9	100.0	100.0
Methicillin susceptible (MSSA)	0.06	0.06	≤0.03-0.25	100.0	100.0	100.0
Coagulase negative staphylococci (14,963)	0.06	0.12	≤0.03-2	99.6	>99.9	>99.9
β-hemolytic streptococci (7,582)	≤0.03	≤0.03	≤0.03-0.25	100.0	100.0	100.0
Viridans Group Streptococci (3,836)	0.06	0.06	≤0.03-0.25	100.0	100.0	100.0
S. pneumoniae (17,340)	≤0.03	≤0.03	≤0.03-0.25	100.0	100.0	100.0
E. faecalis (13,109)	0.06	0.06	≤0.03->4	96.2	96.3	96.4
E. faecium (6,841)	4	>4	≤0.03->4	29.4	32.2	35.7

β-hemolytic streptococci are mainly *S. pyogenes* and *S. agalactiae*; Data from R. Jones, JMI Laboratories, SENTRY database.

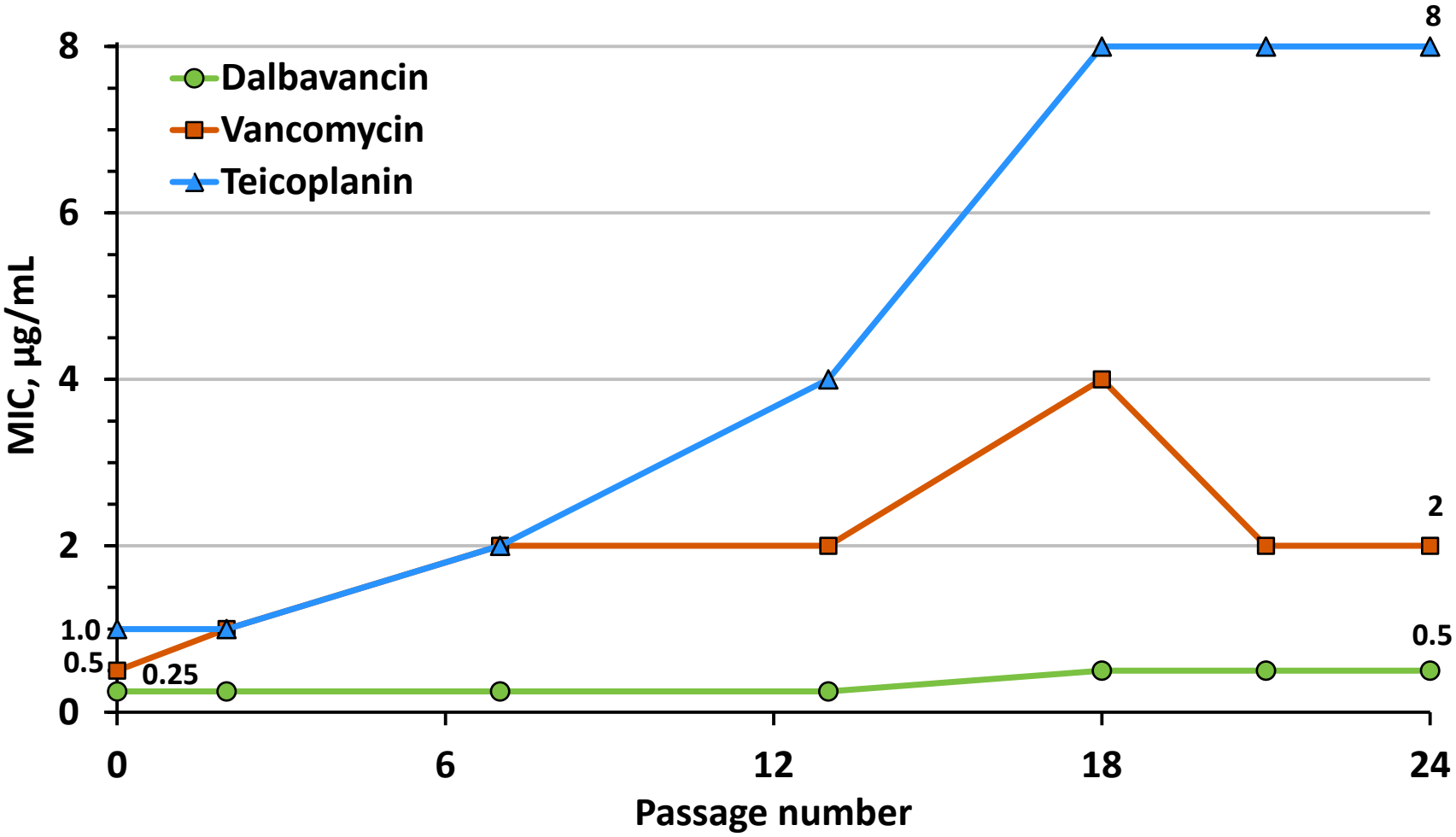
In vitro Activity of Dalbavancin Against *S. aureus*

Comparative activity of dalbavancin against 39,824 isolates of *S. aureus* from the US (2002-2012)

	MIC, µg/mL			% resistant[a]
Antimicrobial agent	**50%**	**90%**	**Range**	**CLSI**
Dalbavancin	0.06	0.06	≤0.03 - 0.5	—
Vancomycin	1	1	≤0.12 - 4	0.0
Oxacillin	>2	>2	≤0.25 - >2	52.5
Erythromycin	>2	>2	≤0.25 - >2	63.2
Clindamycin	≤0.25	>2	≤0.25 - >2	23.3
Daptomycin	0.25	0.5	≤0.12 - 4	0.0
Levofloxacin	≤0.5	>4	≤0.5 - >4	42.3
Linezolid	1	2	≤0.25 - >8	<0.1
Tetracycline	≤4	≤4	≤4 - >8	4.4

[a] **Criteria as published by CLSI 2013; Data from R. Jones, JMI Laboratories, SENTRY database.**

Resistance Is Not Observed During Serial Passage



Passage experiments performed with *S. aureus* ATCC 25923.

Toxicology Summary

- Toxicology program
  - Species: Rats and dogs
  - NOAEL (28 day): 5× human exposure (mg/kg/day)
  - Target organs: Kidney and liver
- Genotoxicity: none
- Carcinogenicity: not done
- Teratogenicity: none
- Reproductive studies:
  - Impaired fertility in rat not observed at 1.2 × human dose

NOAEL=No Observed Adverse Effect Level.

Dalbavancin Pharmacology

Dalbavancin pharmacokinetic parameters of single 1000-mg dose in healthy subjects

Parameter	Mean (% CV)
C_{max} (mg/L)	287 (13.9)
$AUC_{0\text{-}24}$ (mg·h/L)	3185 (12.8)
$AUC_{0\text{-}Day7}$ (mg·h/L)	11160 (41.1)
Terminal $t_{1/2}$ (h)	346 (16.5)
CL (L/h)	0.0513 (46.8)

- Drug AUC exposure increased proportionally with dose
- Dalbavancin has a low potential for drug-drug interactions
  - Dalbavancin is not significantly metabolized
  - Dalbavancin is not a substrate, inducer, or inhibitor of cytochrome P450 isoenzymes
- Dose reduction of 25% of patients with CrCl <30 mL/min to 750 mg Day 1 and 375 mg Day 8
  - No change in dose for patients on dialysis or patients with hepatic insufficiency
- 93% protein bound
- No effect on the QTc interval
- No impact on GI flora

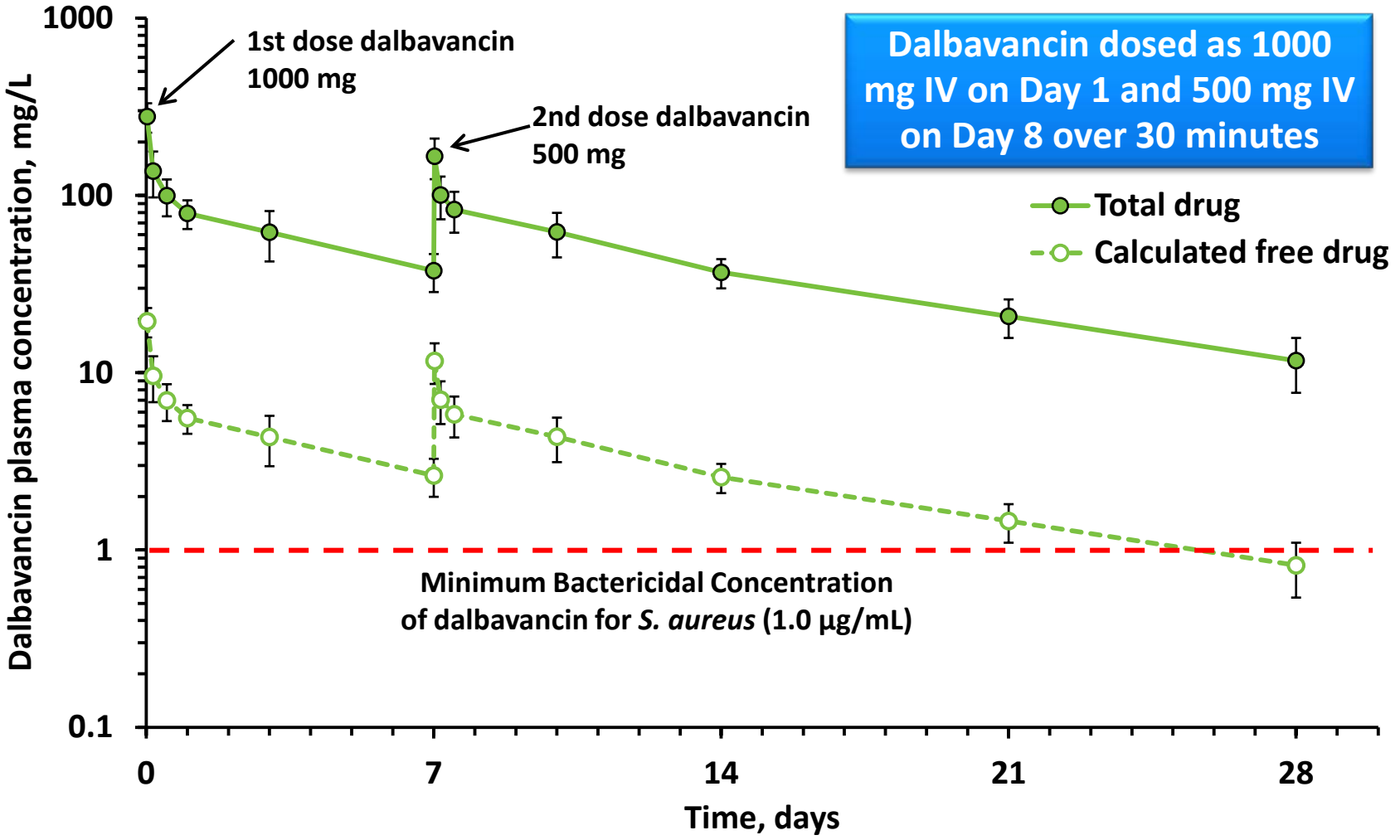
Dose Rationale

Serum exposure after 1000-mg dose on Day 1 and 500-mg dose on Day 8 provides bactericidal levels against *S. aureus* for >14 days

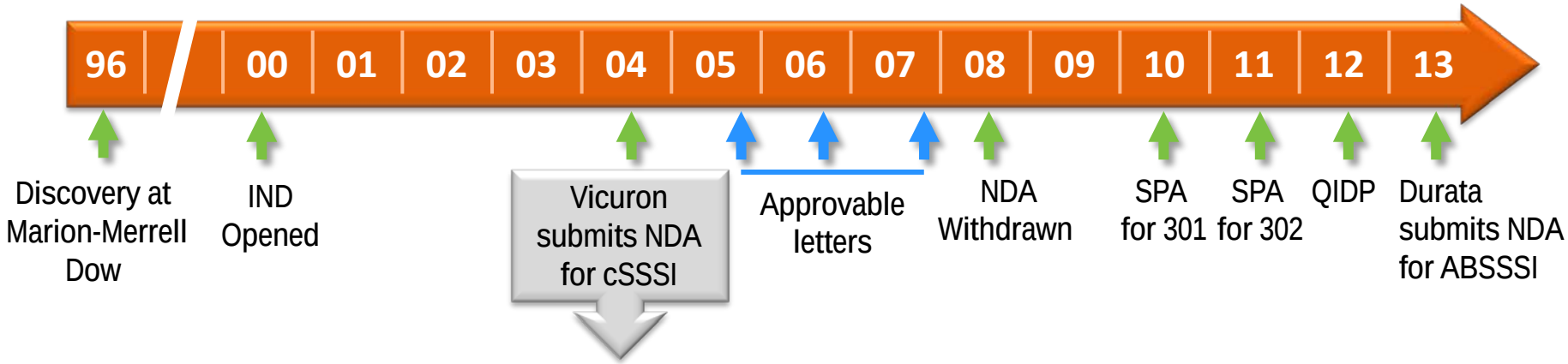
- Minimum bactericidal concentration ≤1.0 µg/mL of free drug
- Proposed dose achieves free drug levels >1.0 µg/mL at Day 14
  - Total drug concentrations are >20 µg/mL at Day 14
    - Protein binding ~ 93% so free drug levels are > 1.0 µg/mL
  - Total serum concentrations >10 µg/mL were bactericidal
- AUC/MIC is the best predictor of efficacy
  - In animal experiments, same total dose was more efficacious when administered as larger, less frequent doses, typical of a long half-life drug in which AUC/MIC best predicts outcome
- Two dose regimen was selected because in VER001-5, 2 doses appeared to be more effective than 1100 mg alone

	1100 mg alone	1000 mg/500 mg
Success	8/13 (61.5%)	16/21 (76.2%)

Once-Weekly Dosing Regimen of Dalbavancin



Discovery, Development, and Regulatory History of Dalbavancin



- **1200 patients treated with dalbavancin in eight Phase 1, two phase 2, and three phase 3 studies**
- **VER001-9 – pivotal study met primary endpoint**
- **Randomized, double-blind, multi-center study**
- **IV dalbavancin: 1000 mg on Day 1, 500 mg on Day 8 vs IV/oral linezolid for 14 days**
- **Investigator assessment of clinical success in Clinically Evaluable population at Day 28; NI delta –12.5%**

Dalbavancin	Linezolid	Difference (95% CI)
386/434 (88.9)	206/226 (91.2)	–2.2 (–7.3, 2.9)

Efficacy

Michael Dunne, MD

Chief Medical Officer

Durata Therapeutics, Inc.

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Clinical Development Program

Studies	Study objective
Phase 1	
Single-dose studies	PK, distribution, excretion, 1500 mg, tissue level, GI flora, QT
Multiple-dose studies	Renal and hepatic impairment, Japanese
Phase 2	
VER001-4	Catheter related blood stream infections
VER001-5	1100 mg single dose vs 1000 mg followed by 500 mg vs physician designated comparator
Phase 3	
Uncomplicated Skin Infection	
VER001-8	Dalbavancin vs Cefazolin/Cephalexin
Complicated Skin Infection	
VER001-16	Skin Infection due to MRSA; Dalbavancin vs Vancomycin/Cephalexin
VER001-9	Dalbavancin vs linezolid
Acute Bacterial Skin and Skin Structure Infection	
DUR001-301	Dalbavancin vs Vancomycin/linezolid
DUR001-302	Dalbavancin vs Vancomycin/linezolid

Clinical Development Program

	Dalbavancin	Dalbavancin proposed dose	Active comparator	Placebo	Total
Total Phase 1, 2, and 3 studies	**2092**	**1785**	**1276**	**74**	**3442**
Phase 1 studies	**307**	NA	**50**	**74**	**431**
Single-dose studies	238	NA	50	59	347
Multiple-dose studies	69	27	0	15	84
Phase 2 studies	**81**	**54**	**55**	**0**	**136**
VER001-4	40	33	34	0	74
VER001-5	41	21	21	0	62
Phase 3 studies	**1704**	**1704**	**1171**	**0**	**2875**
Uncomplicated Skin Infection					
VER001-8	367	367	186	0	553
Complicated Skin Infection					
VER001-16	107	107	49	0	156
VER001-9	571	571	283	0	854
Acute Bacterial Skin and Skin Structure Infection					
DUR001-301	288	288	285	0	573
DUR001-302	371	371	368	0	739

Acute Bacterial Skin and Skin Structure Infections

Studies DUR001-301/302

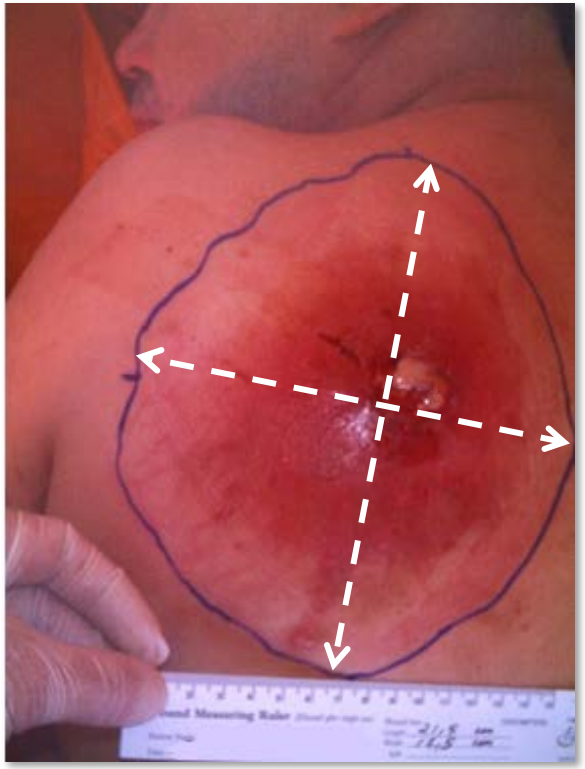
Key Inclusion Criteria
Studies DUR001-301/302

- ABSSSI involves deep soft tissue associated with area of erythema >75 cm^2
  - Cellulitis
  - Major cutaneous abscess
    - Required I&D and 5 cm margin of erythema around abscess
  - Surgical site or traumatic wound infection
    - Required 5 cm margin of erythema from edge of wound
- At least ONE of the following systemic signs of infection:
  - Fever (≥38°C/100.4°F within 24 hours of baseline)
  - Leukocytosis (WBC count >12,000 cells/mm^3)
  - Left shift (peripheral smear with ≥10% band forms)
- In addition to erythema, at least TWO of the following signs of ABSSSI
  - Purulent drainage/discharge, fluctuance, heat/localized warmth, tenderness to palpation, swelling/induration
- Infection severity such that a minimum of 3 days of IV therapy is appropriate

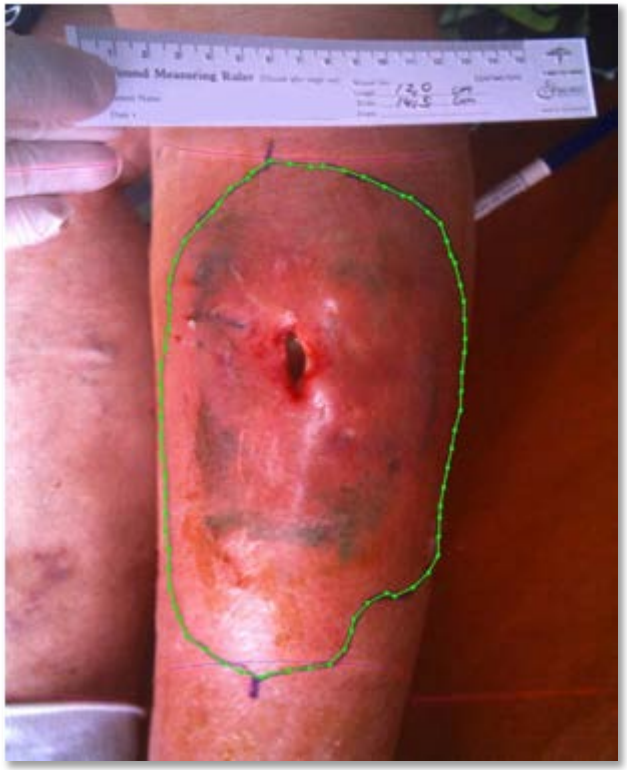
Key Exclusion Criteria
Studies DUR001-301/302

- Prior antibiotic, systemically or topically administered, 14 days prior to randomization
- Gram-negative bacteremia
- Burns
- Diabetic foot infection
- Decubitus ulcer
- Infected device
- Venous catheter entry site infection

ABSSSI from Dalbavancin Clinical Program



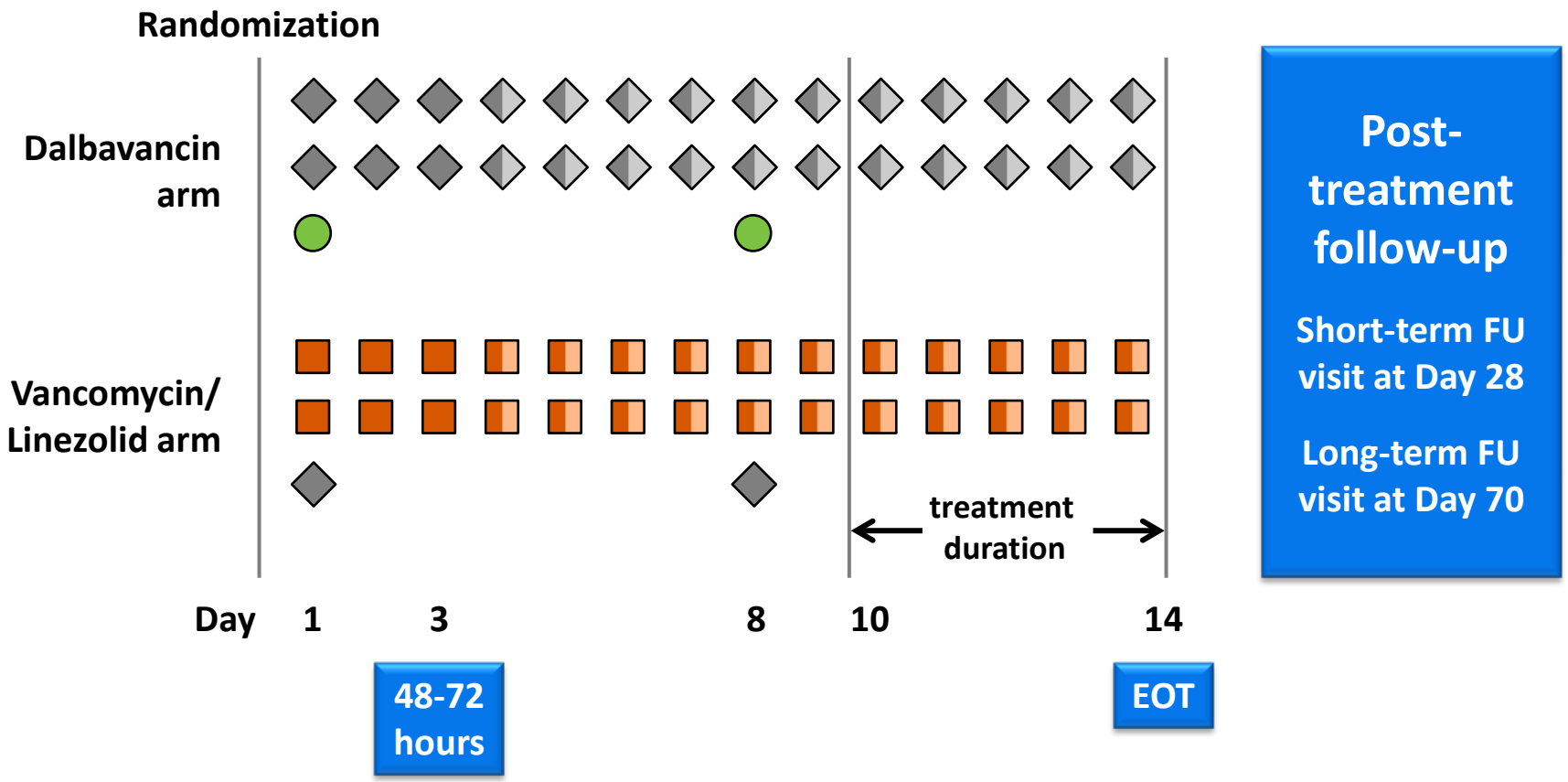
Left back scapular region



Anterior left lower leg

Study Design

Studies DUR001-301/302



Study Endpoints
Studies DUR001-301/302

Primary endpoint

- Early response at 48 to 72 hr post-initiation of therapy
  - Cessation of spread of the erythema of the lesion, and
  - Absence of fever (in 3 sequential temps taken q6h)
- Non-inferiority if lower limit of 95% confidence interval on the difference exceeds –10%

Secondary endpoints

- Clinical status at end of therapy (EOT) (Day 14) in clinically evaluable (CE) and intent-to-treat (ITT) populations
- Prespecified Sensitivity Analyses for Clinical Status at EOT and SFU
- Clinical status at short-term follow-up (SFU) (Day 28), CE, and ITT populations
- Investigator assessments at EOT and SFU
- Microbiologic outcome

Demographics

Patient Demographics
Studies DUR001-301/302

	DUR001-301		DUR001-302	
	Dalbavancin N=288	Vancomycin/ Linezolid N=285	Dalbavancin N=371	Vancomycin/ Linezolid N=368
Gender, n (%)				
Male	170 (59.0)	173 (60.7)	223 (60.1)	201 (54.6)
Age, yr				
Mean	48.8	48.9	49.1	51.4
Range	18 - 84	18 - 84	18 – 85	18 – 84
Race or ethnic group, n (%)				
White	264 (91.7)	259 (90.9)	328 (88.4)	320 (87.0)
Black or African American	16 (5.6)	19 (6.7)	13 (3.5)	17 (4.6)
Asian	1 (0.3)	2 (0.7)	27 (7.3)	30 (8.2)
Other	7 (2.4)	5 (1.8)	3 (0.8)	1 (0.3)
Region of enrollment, n, (%)				
United States/Canada	123 (42.7)	121 (42.5)	115 (31.0)	114 (31.0)
Europe, S Africa and Asia	165 (57.3)	164 (57.5)	256 (69.0)	254 (69.0)

Patient Demographics
Studies DUR001-301/302

	Patients, n/N (%)			
	DUR001-301		DUR001-302	
	Dalbavancin N=288	Vancomycin/ Linezolid N=285	Dalbavancin N=371	Vancomycin/ Linezolid N=368
Temperature ≥38°C	243/284 (85.6)	242/284 (85.2)	306/365 (83.8)	310/365 (84.9)
WBC >12,000 cells/mm^3	98/259 (37.8)	104/254 (40.9)	149/368 (40.5)	146/367 (39.8)
Bands ≥10%	63/238 (26.5)	66/244 (27.0)	48/241 (19.9)	42/234 (17.9)
Elevated hs-CRP, mg/L	253/284 (89.1)	258/284 (90.8)	332/366 (90.7)	327/367 (89.1)
SIRS criteria met	175/284 (61.6)	175/284 (61.6)	157/368 (42.7)	161/368 (43.8)

Patient Demographics
Studies DUR001-301/302

	DUR001-301		DUR001-302	
	Dalbavancin N=288	Vancomycin/ Linezolid N=285	Dalbavancin N=371	Vancomycin/ Linezolid N=368
Diabetes				
History, %[a]	14.9	10.5	9.4	16.8
Elevated Fasting glucose [b]	39.2	41.4	38.5	37.5
BMI kg/m^2 , median (range)	28 (14, 69)	27 (18, 65)	27 (17, 61)	28 (17, 61)
Lesion size				
Median area, cm^2 (range)	333.0 (26 - 3400)	367.8 (78 - 3675)	313.50 (85 - 5100)	362.40 (72 - 3922)
Infection type, n (%)				
Cellulitis	156 (54.2)	147 (51.6)	198 (53.4)	202 (54.9)
Major abscess	72 (25.0)	86 (30.2)	90 (24.3)	87 (23.6)
Traumatic/surgical infection	60 (20.8)	52 (18.2)	82 (22.1)	79 (21.5)
Pathogen at baseline, n (%)	153 (53.1)	155 (54.4)	184 (49.6)	174 (47.3)
MRSA	44 (28.8)	39 (25.2)	46 (25.0)	28 (16.1)

[a] For DUR001-302, p=0.003 for difference in history of diabetes mellitus; [b] diagnostic of prediabetes/diabetes.

Mean Duration of Therapy by Treatment Group

Studies DUR001-301/302

Study drug therapy	Mean duration of IV and oral therapy, days			
	Study DUR001-301		Study DUR001-302	
	Dalbavancin N=284	Vancomycin/ Linezolid N=284	Dalbavancin N=368	Vancomycin/ Linezolid N=367
IV drug	4.8	4.8	3.8	3.8
Oral drug	5.2	5.5	6.4	6.5
Total drug	**10.6**	**11.0**	**11.1**	**11.1**

- IV drug was either active or placebo vancomycin
- Oral drug was either active or placebo linezolid

Clinical Outcome

Primary Endpoint
Studies DUR001-301/302

	Patients, n (%)			
	DUR001-301		DUR001-302	
	Dalbavancin N=288	Vancomycin/ Linezolid N=285	Dalbavancin N=371	Vancomycin/ Linezolid N=368
Clinical responder	240 (83.3)	233 (81.8)	285 (76.8)	288 (78.3)
Clinical non-responder	48 (16.7)	52 (18.2)	86 (23.2)	80 (21.7)
Difference (95% CI)	1.5 (–4.6, 7.9)		–1.5 (–7.4, 4.6)	

In both studies, dalbavancin was found to be non-inferior to vancomycin/linezolid

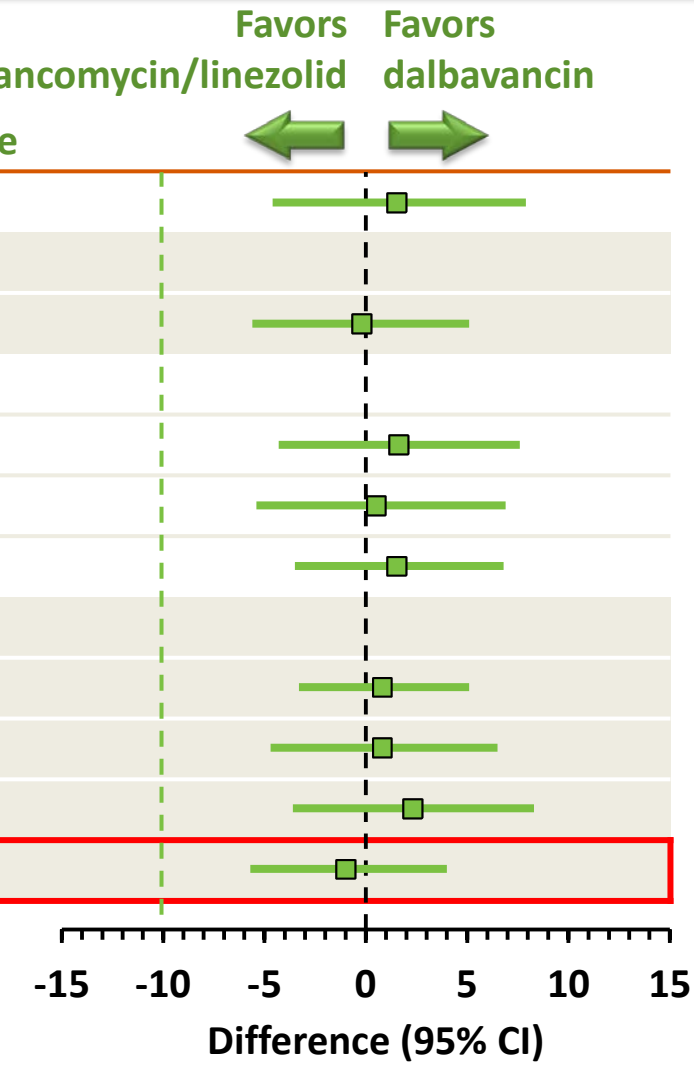
Reasons for Failure at 48-72 hr

Studies DUR001-301/302—ITT Population

	Dalbavancin N=659	Vancomycin/ Linezolid N=653
Area of infection greater than baseline	41	33
Temperature >37.6°C	41	43
Both increased infection size and temperature >37.6°C	8	7
Died within first 72 hours	0	1
Non-study antibiotic added within the first 72 hours	6	7
Randomized but not treated	7	2
Missing data	55	52
Missing temperature or lesion size measurements	22	21
No fever, but criteria for temperature documentation not met	33	31

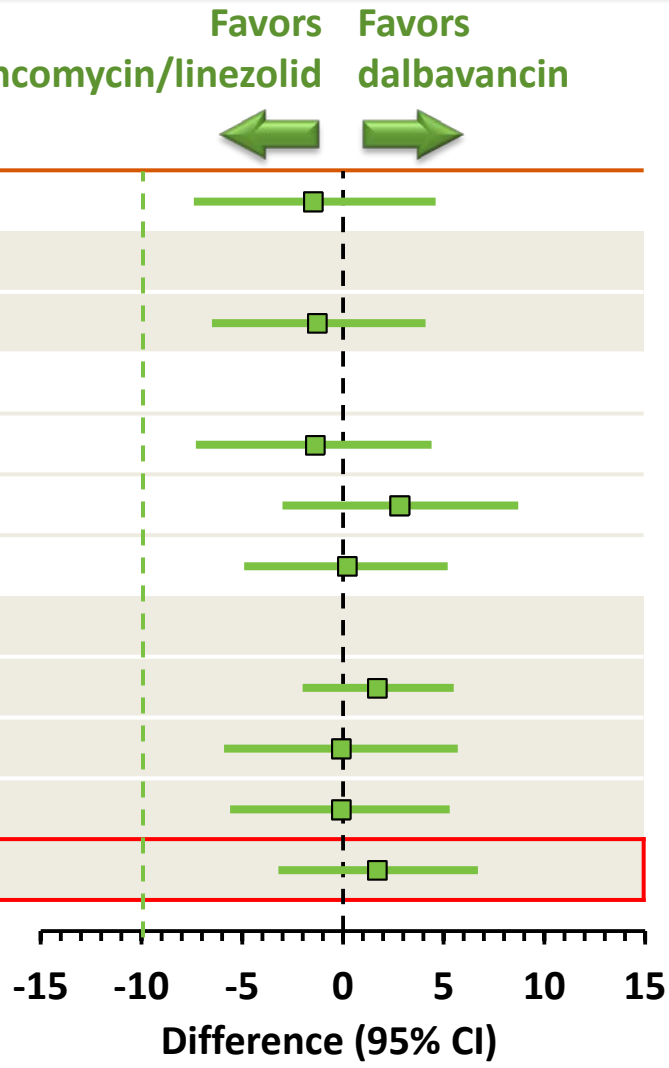
Primary Endpoint Assessments
Prespecified Sensitivity Analyses
Study DUR001-301

Assessments	DAL, %	V/L, %	Difference
Primary endpoint	**83.3**	**81.8**	**1.5**
Missing data sensitivity analyses			
Missing data as responders	88.2	88.4	–0.2
Alternative definitions for absence of fever			
3 sequential temps <q 12 hr	85.1	83.5	1.6
Only first temp within 48-72 hr	82.3	81.8	0.5
2 temps in 48-72 hr	89.6	88.1	1.5
Alternative primary endpoints			
Absence of fever, alone	87.5	86.7	0.8
Cessation of spread, alone	93.8	93.0	0.8
≥10% reduction area; <l,<w	85.8	83.5	2.3
≥20% reduction in lesion	89.9	90.9	–1.0



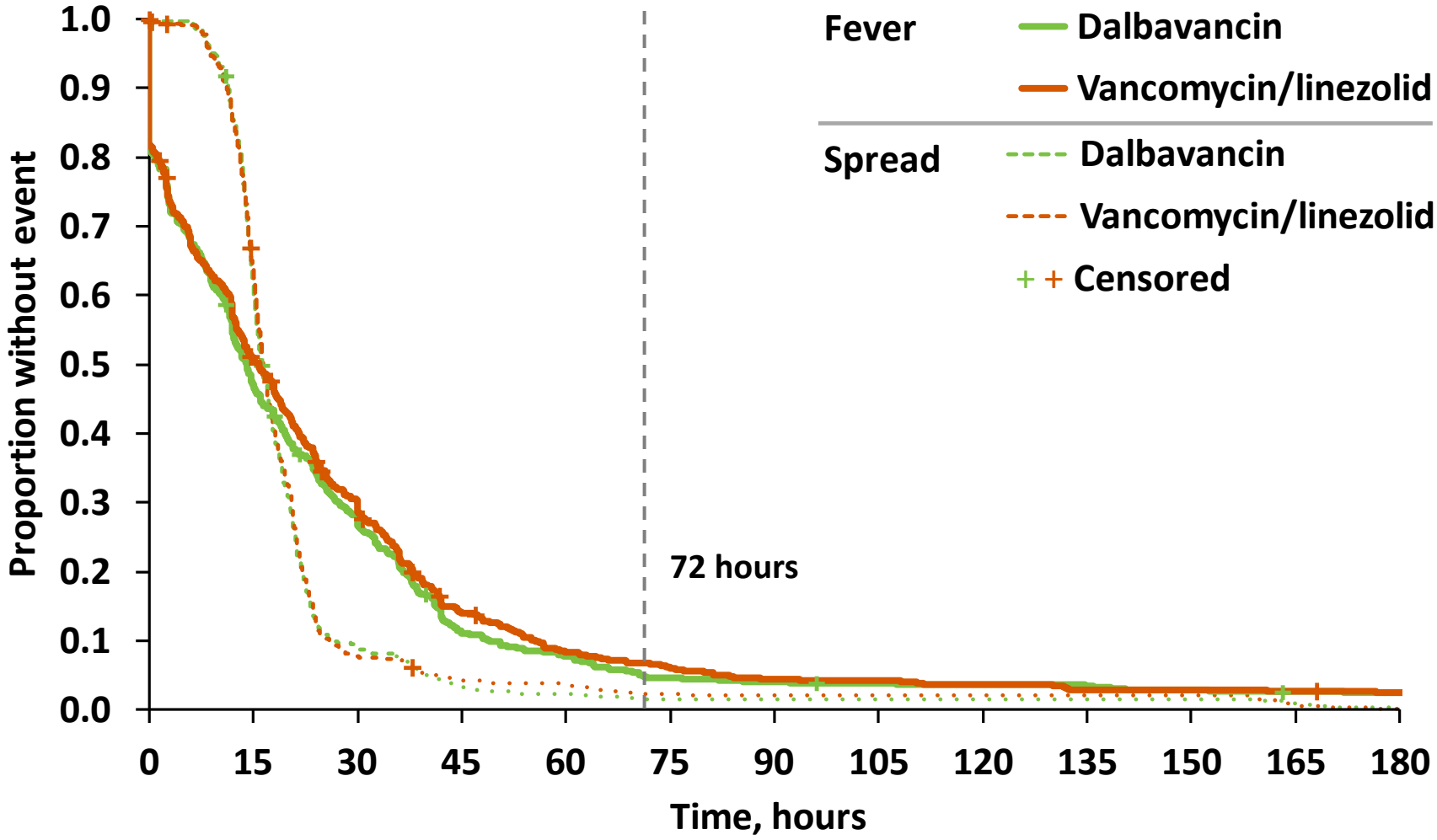
Primary Endpoint Assessments
Prespecified Sensitivity Analyses
Study DUR001-302

Assessments	DAL, %	V/L, %	Difference
Primary endpoint	**76.8**	**78.3**	**–1.5**
Missing data sensitivity analyses			
Missing data as responders	83.8	85.1	–1.3
Alternative definitions for absence of fever			
3 sequential temps <q 12 hr	79.0	80.4	–1.4
Only first temp within 48-72 hr	81.1	78.3	2.8
2 temps in 48-72 hr	86.3	86.1	0.2
Alternative primary endpoints			
Cessation of spread, alone	94.1	92.4	1.7
≥10% reduction in lesion, <l,<w	79.8	79.9	–0.1
Absence of fever, alone	83.3	83.4	–0.1
≥20% reduction in lesion	87.6	85.9	1.7



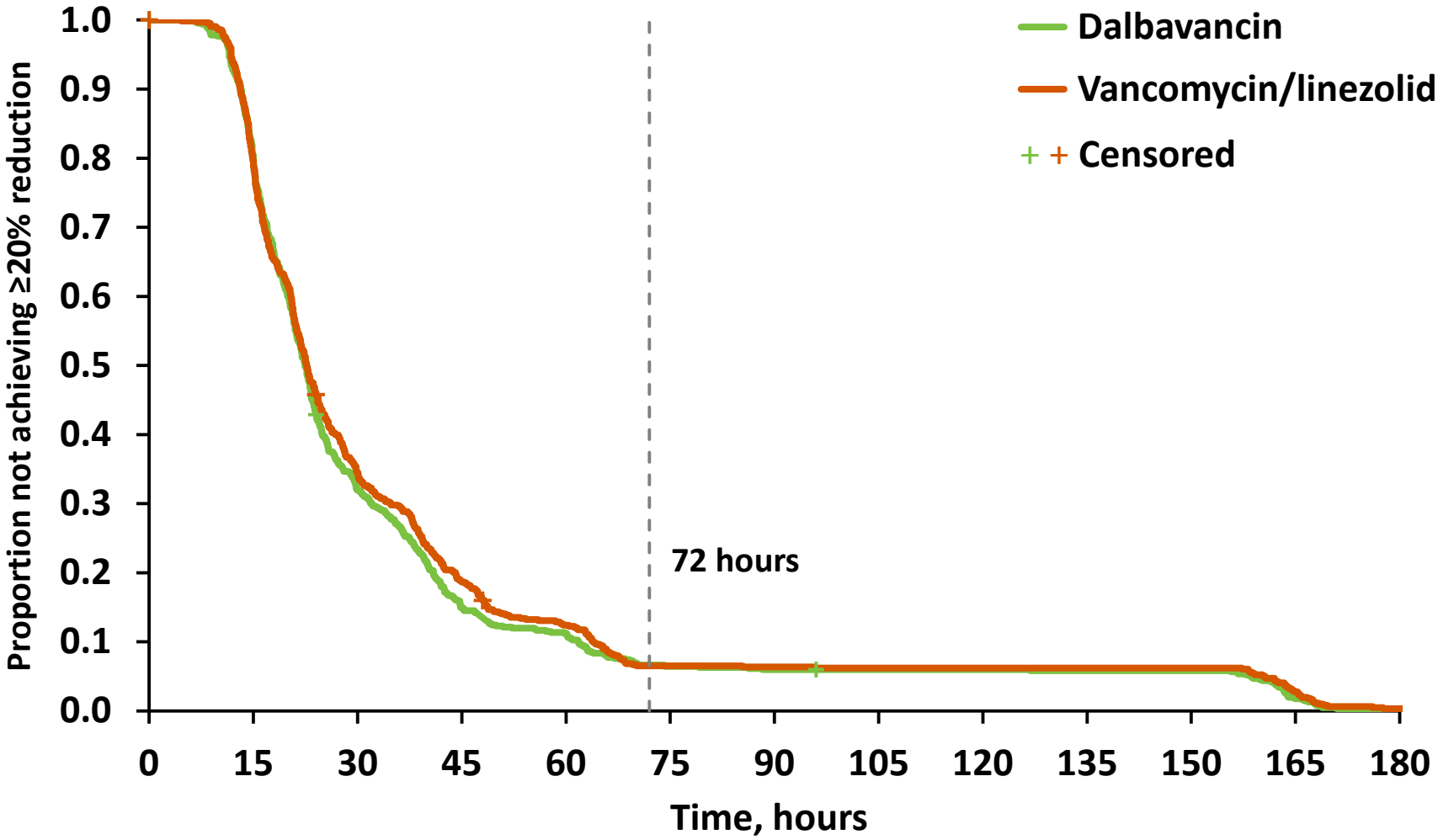
Time to Absence of Fever or Cessation of Spread

Studies DUR001-301/302 Pooled



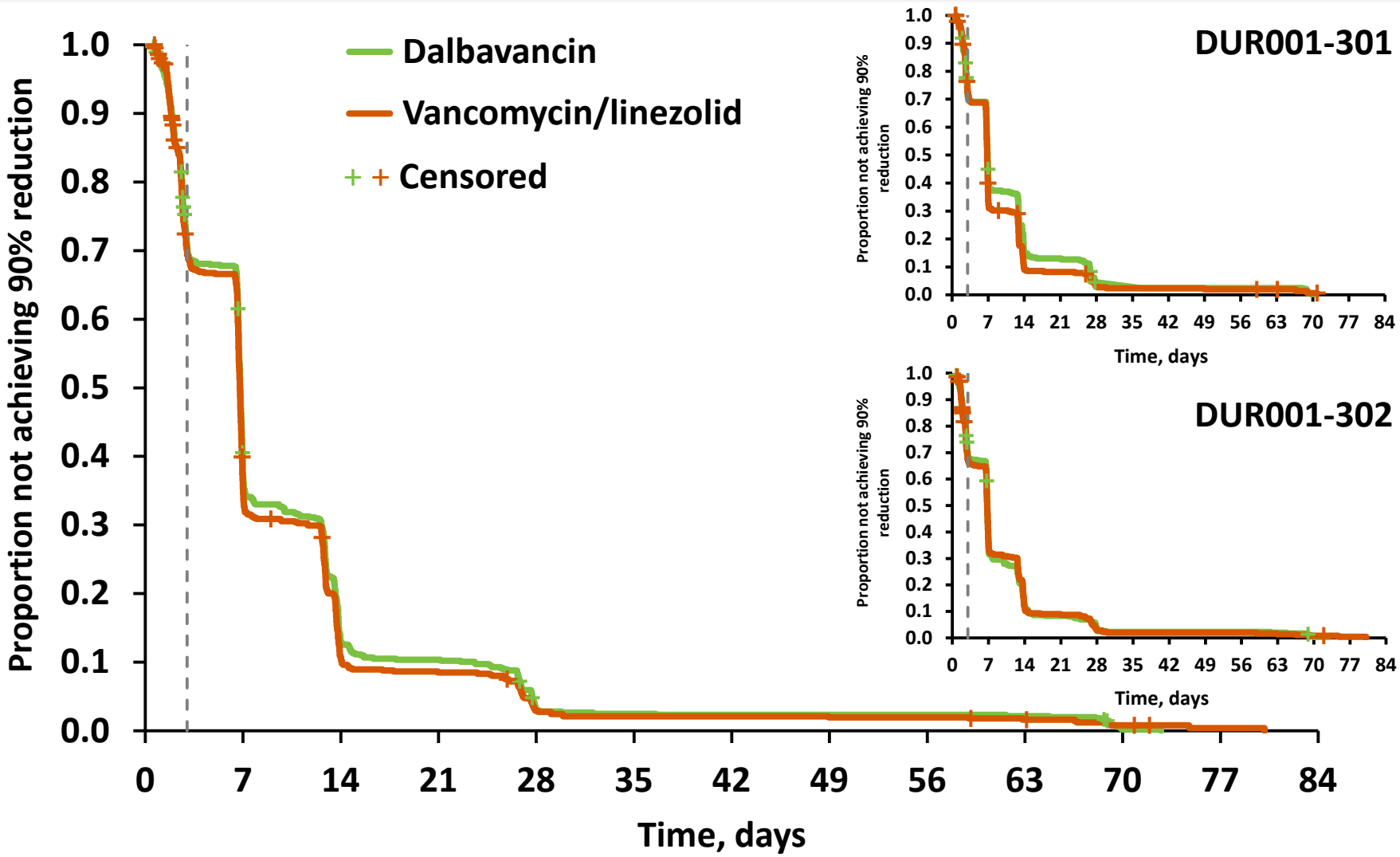
Time to ≥20% Reduction in Lesion Size

Studies DUR001-301/302 Pooled



Time to 90% Reduction in Lesion Size

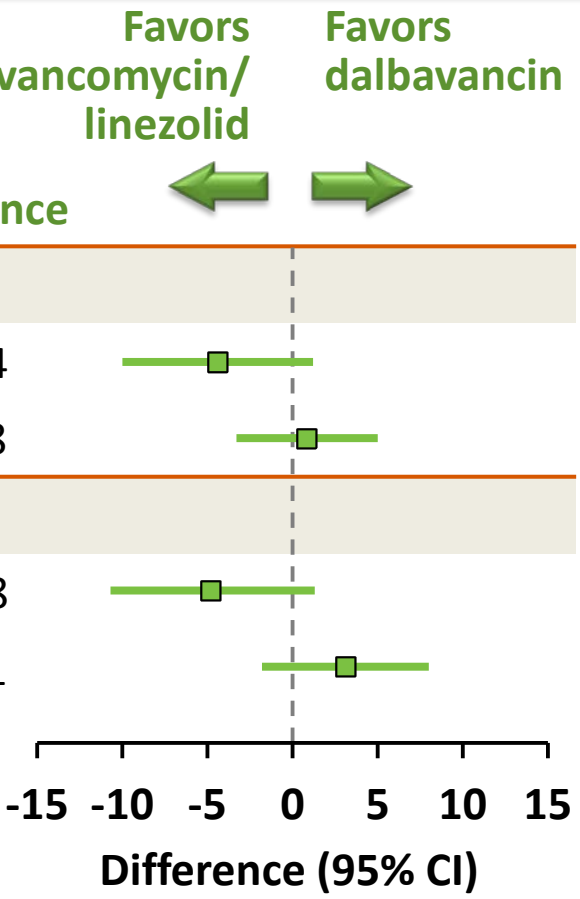
Studies DUR001-301/302



Clinical Status at End of Treatment

Studies DUR001-301/302

Analysis	Patients, n/N (%) Dalbavancin	Vancomycin/ linezolid	Difference
CE clinical status of success			
DUR001-301	214/246 (87.0)	222/243 (91.4)	–4.4
DUR001-302	303/324 (93.5)	280/302 (92.7)	0.8
ITT clinical status of success			
DUR001-301	236/288 (81.9)	247/285 (86.7)	–4.8
DUR001-302	329/371 (88.7)	315/368 (85.6)	3.1



Clinical Outcomes at End of Treatment

Study DUR001-301

Study population	Patients, n (%) Dalbavancin	Vancomycin/ Linezolid	Difference (95% CI)
CE	246	243	
Clinical status[a]	214 (87.0)	222 (91.4)	–4.4 (–10.0, 1.2)
Clinical status – sensitivity analysis[b]	230 (93.5)	230 (94.7)	–1.2 (–6.6, 3.2)
Investigator's response of success	233 (94.7)	237 (97.5)	–2.8 (–6.7, 0.7)
ITT	288	285	
Clinical status[a]	236 (81.9)	247 (86.7)	–4.8 (–10.7, 1.3)
Clinical status – sensitivity analysis[b]	253 (87.8)	255 (89.5)	–1.7 (–6.9, 3.6)
Investigator's response of success	260 (90.3)	262 (91.9)	–1.6 (–6.5, 3.1)

[a] FDA's analysis required reduction in length and width as well as lesion area.
[b] Prespecified analysis: success if warmth was reduced from baseline rather than completely resolved.

Clinical Outcomes at End of Treatment
DUR001-302

Study population	Patients, n (%) Dalbavancin	Vancomycin/ Linezolid	Difference (95% CI)
CE	324	302	
Clinical status[a]	303 (93.5)	280 (92.7)	0.8 (–3.2, 5.0)
Clinical status – sensitivity analysis[b]	303 (93.5)	287 (95.0)	–1.5 (–5.3, 2.3)
Investigator's response of success	314 (96.9)	290 (96.0)	0.9 (–2.1, 4.1)
ITT	371	368	
Clinical status[a]	329 (88.7)	315 (85.6)	3.1 (–1.8, 8.0)
Clinical status – sensitivity analysis[b]	332 (89.5)	322 (87.5)	2.0 (–2.7, 6.7)
Investigator's response of success	342 (92.2)	332 (90.2)	2.0 (–2.2, 6.2)

[a] FDA's analysis required reduction in length and width as well as lesion area.
[b] Prespecified analysis: success if warmth was reduced from baseline rather than completely resolved.

Clinical Success According to Infection Type

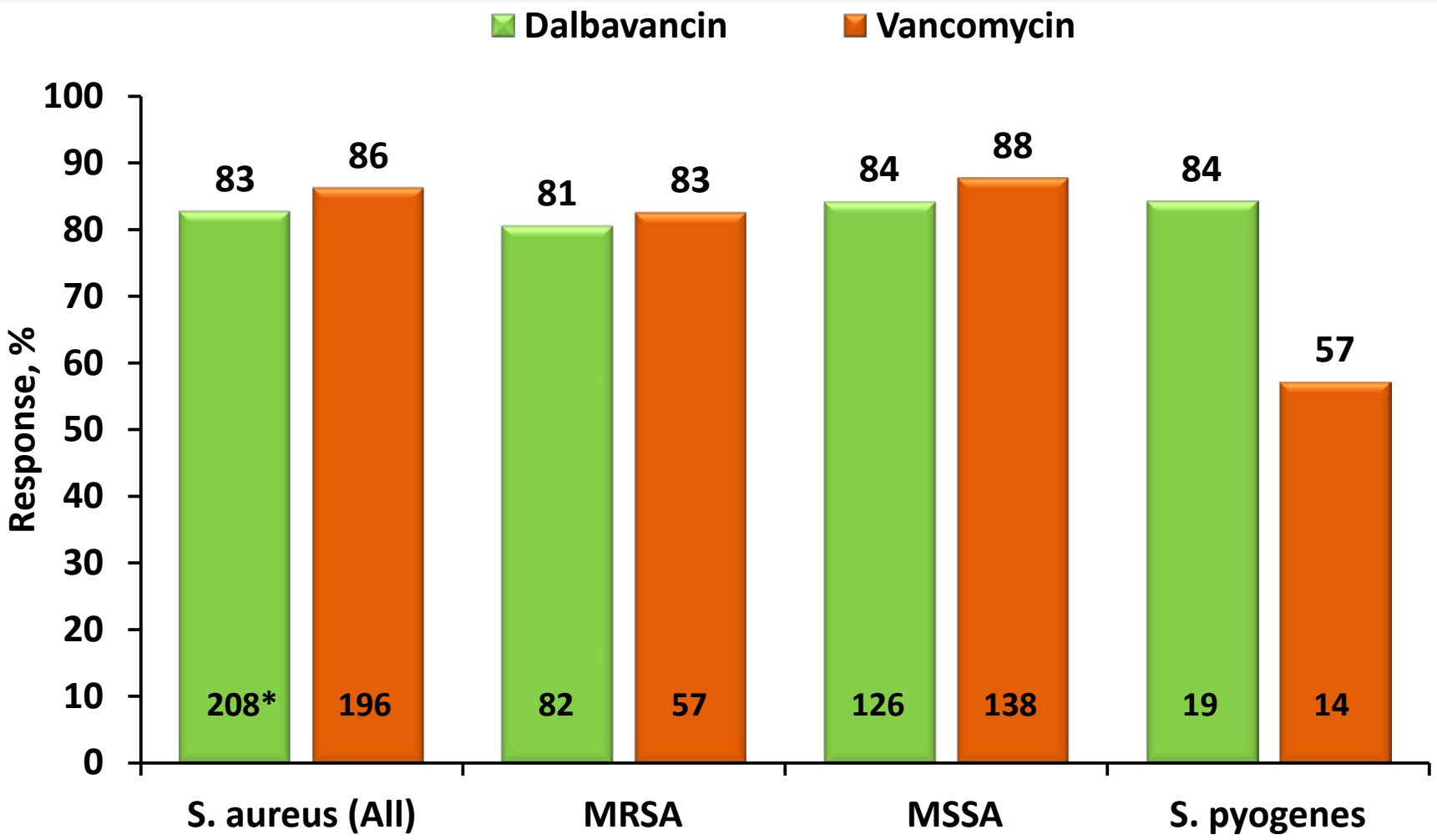
Studies DUR001-301/302 Pooled

	Patients, n/N (%)	
	Dalbavancin	Vancomycin/ Linezolid
Cellulitis		
48-72 hours (ITT population)	281/354 (79.4)	269/349 (77.1)
Clinical status at end of therapy (CE population)	294/324 (90.7)	276/301 (91.7)
Major abscess		
48-72 hours (ITT population)	133/163 (81.6)	149/173 (86.1)
Clinical status at end of therapy (CE population)	125/133 (94.0)	133/139 (95.7)
Traumatic wound/surgical site infection		
48-72 hours (ITT population)	111/142 (78.2)	103/131 (78.6)
Clinical status at end of therapy (CE population)	98/113 (86.7)	93/105 (88.6)

Microbiologic Outcome

Clinical Success at the Primary Endpoint, at 48-72 Hours, by Pathogen

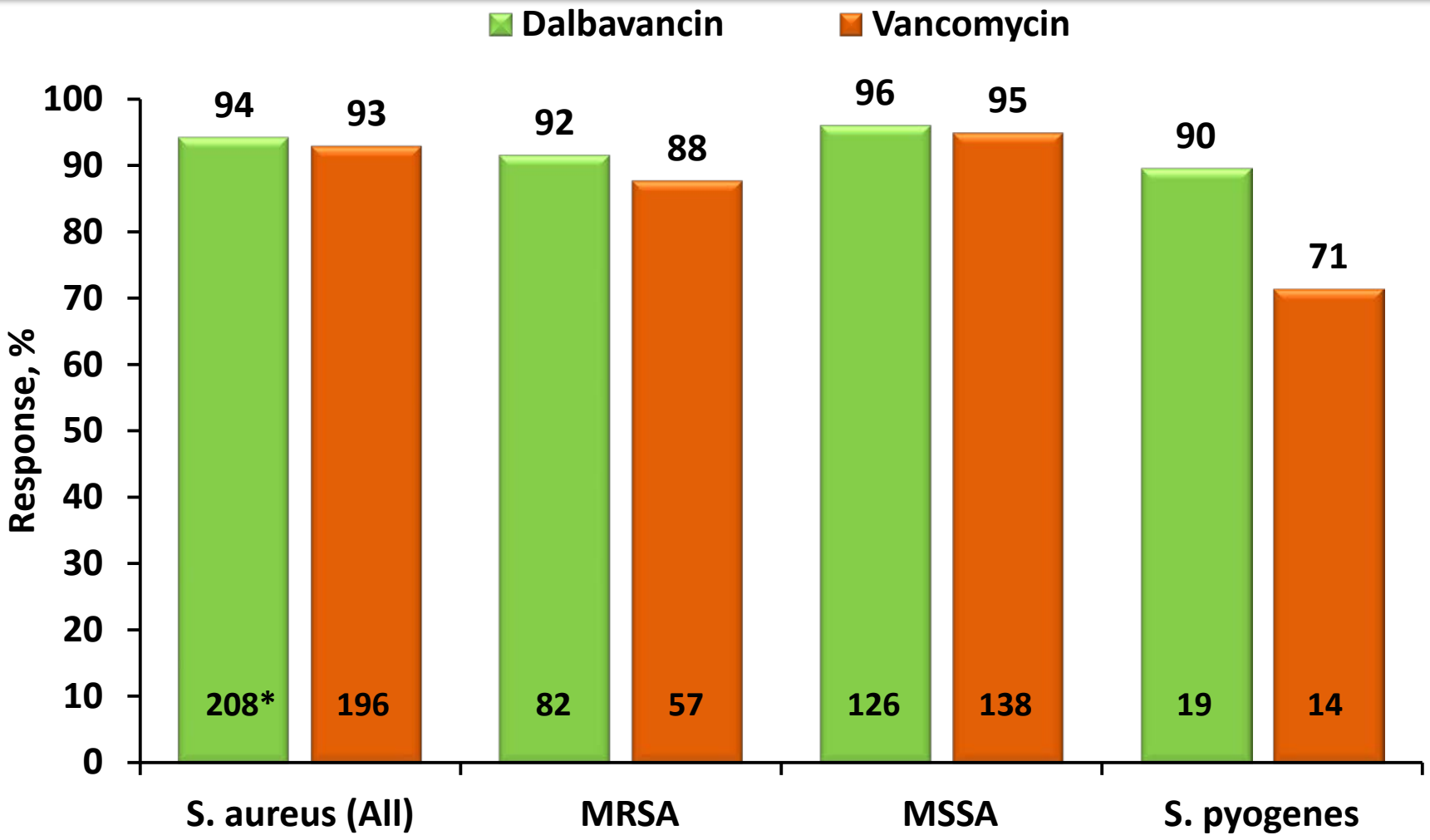
Studies DUR001-301/302 Pooled



*Number of patients.

≥20% Reduction in Lesion Size at 48-72 Hours by Pathogen

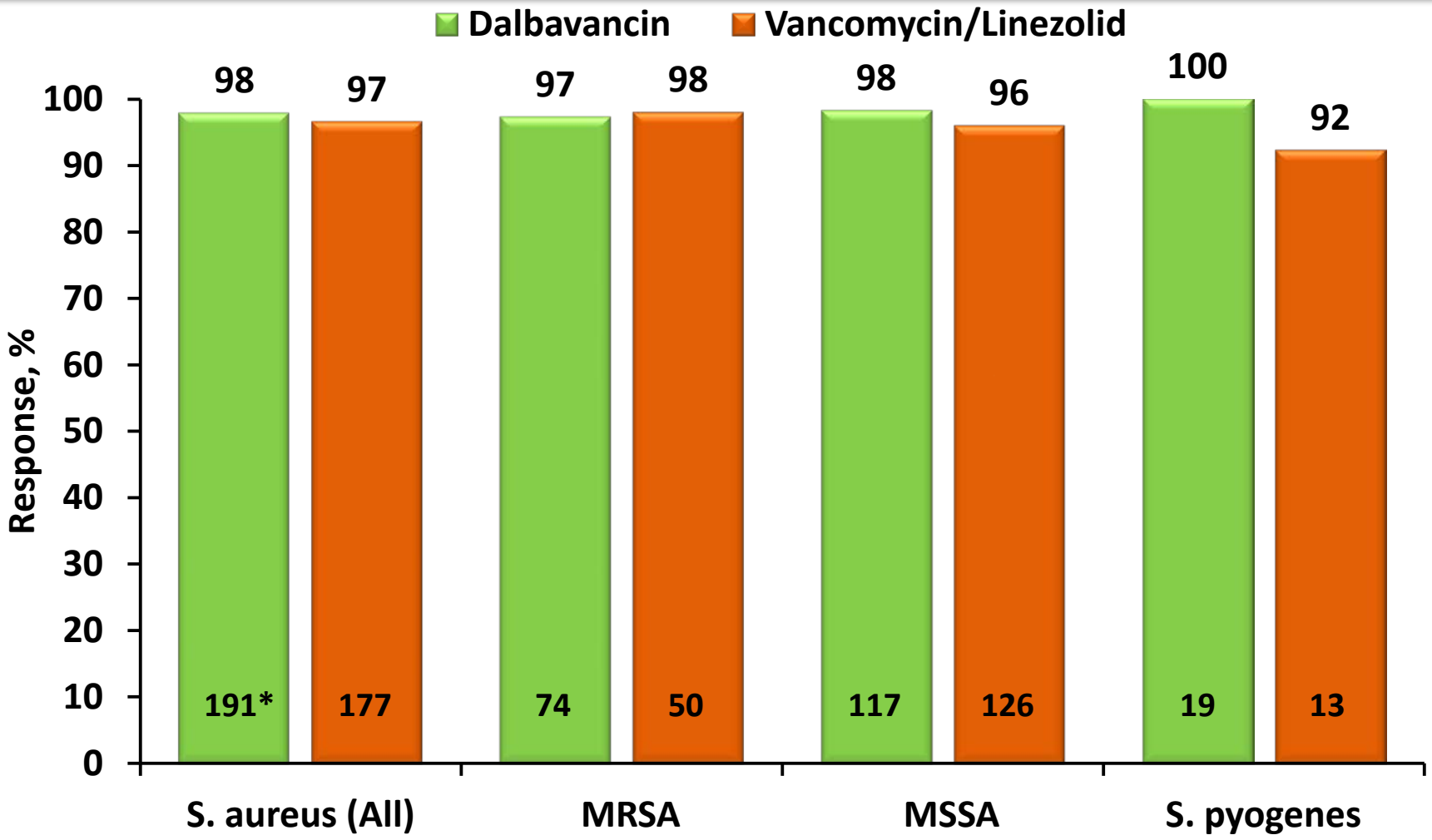
Studies DUR001-301/302 Pooled



*Number of patients.

Clinical Success by Baseline Pathogen Investigator Assessment at End of Treatment (ME)

Studies DUR001-301/302 Pooled



*Number of patients.

Documented Clearance and Clinical Outcome *S. aureus* Bacteremia

Phase 2/3

	Dalbavancin				Comparator			
		Early response		EOT		Early response		EOT
Infection	Clearance of bacteremia[a]	Cessation/ fever	≥ 20% reduction	Clinical success[b]	Clearance of bacteremia	Cessation/ fever	≥20% reduction	Clinical success
ABSSSI								
DUR001-301	3/3	3/4	3/4	2/3	2/3	2/4	2/4	3/3
DUR001-302	7/7	11/12	9/12	5/6	6/6	6/7	6/7	5/6
cSSSI								
VER001-9	4/4	—	—	3/4	2/2	—	—	2/2
Catheter-related bloodstream infection								
VER001-4	10/10	—	—	9/9	9/9	—	—	8/12
Total	**24/24 (100%)**	**14/16 (87.5%)**	**12/16 (75%)**	**19/22 (86.4%)**	**19/20 (95%)**	**8/11 (72.7%)**	**8/11 (72.7%)**	**18/23 (78.3%)**

[a] Patients with follow-up blood culture (post-baseline).
[b] Clinically evaluable population (those with missing data excluded from analysis) of patients with a positive blood culture at baseline and a follow-up blood culture.

Consistent, Robust Efficacy Results Observed in 2 Pivotal Studies in Patients With ABSSSI

- Two large Phase 3 studies were conducted
  - Both under a Special Protocol Agreement
- Dalbavancin met endpoints demonstrating both early efficacy and end-of-treatment cure
- Consistent across multiple sensitivity analyses, time points, clinical variables, different patient populations, and methods of clinical assessment
- Robust efficacy was demonstrated across all infection subtypes typically observed in patients

Safety

Sailaja Puttagunta, MD

Executive Medical Director
Durata Therapeutics, Inc.

DURATA
THERAPEUTICS®

Summary of Treatment-emergent Adverse Events
Studies DUR001-301/302 Pooled and Phase 2/3

	Patients, n (%)			
	DUR001-301/302 pooled		Phase 2/3	
	Dalbavancin N=652	Vancomycin/ linezolid N=651	Dalbavancin N=1778	Comparator N=1224
Treatment-emergent AE	214 (32.8)	247 (37.9)	799 (44.9)	573 (46.8)
Treatment-related AE	80 (12.3)	89 (13.7)	328 (18.4)	246 (20.1)
Serious AE	17 (2.6)	26 (4.0)	109 (6.1)	80 (6.5)
Treatment-related serious AE	2 (0.3)	4 (0.6)	3 (0.2)	9 (0.7)
Discontinuation due to TEAE	14 (2.1)	13 (2.0)	53 (3.0)	35 (2.9)
Died	1 (0.2)	7 (1.1)	10 (0.6)	14 (1.1)

Treatment-related SAEs
Phase 2/3

AE preferred term	Patients, n (%) Dalbavancin N=1778	Comparator N=1224
≥1 treatment-related SAE	**3 (0.2)**	**9 (0.7)**
Leukopenia	1 (0.1)	0
Anaphylactoid reaction	1 (0.1)	0
Cellulitis	1 (0.1)	1 (0.1)
Renal failure acute	0	2 (0.2)
Gastrointestinal disorder	0	1 (0.1)
Face edema	0	1 (0.1)
Pancytopenia	0	1 (0.1)
Thrombocytopenia	0	1 (0.1)
Nephropathy toxic	0	1 (0.1)
Pancreatitis acute	0	1 (0.1)

SAE: Anaphylactoid Reaction

- 22-year-old White male, history of reactive airway disease and atopy, treated with 1 dose of IV dalbavancin
- Also received general anesthetic agents ~3 hours earlier and aztreonam intravenously as a bolus immediately prior to start of dalbavancin infusion
- Developed dyspnea, laryngospasm, and hypotension/shock ~15 minutes after start of planned 30 minute IV infusion
- Dalbavancin infusion stopped and patient was treated immediately with epinephrine, midazolam, antihistamines and a 5 day course of prednisone
- Symptoms and signs associated with event considered to be completely resolved within ~1 hour of initiation of dalbavancin treatment

Treatment-Emergent Adverse Events >2% in Any Treatment Group

Phase 2/3

	Patients, n (%)	
	Dalbavancin N=1778	Comparator N=1224
Treatment-emergent AE		
≥1 TEAE	**799 (44.9)**	**573 (46.8)**
Nausea	98 (5.5)	78 (6.4)
Headache	83 (4.7)	59 (4.8)
Diarrhea	79 (4.4)	72 (5.9)
Constipation	52 (2.9)	30 (2.5)
Vomiting	50 (2.8)	37 (3.0)
Rash	38 (2.1)	22 (1.8)
Urinary tract infection	36 (2.0)	16 (1.3)
Pruritus	32 (1.8)	35 (2.9)
Insomnia	27 (1.5)	30 (2.5)
Treatment- related and treatment-emergent AE		
Nausea	49 (2.8)	40 (3.3)
Diarrhea	45 (2.5)	45 (3.7)
Pruritus	11 (0.6)	23 (1.9)

Adverse Events vs Treatment-Emergent Adverse Events >1% Selected Adverse Events in Any Treatment Group

Studies DUR001-301/302

	FDA		Durata	
	Adverse events		Treatment-emergent adverse events	
Preferred Term	Dalbavancin N=652	Comparator N=651	Dalbavancin N=652	Comparator N=651
Nausea	29 (4.4)	32 (4.9)	27 (4.1)	28 (4.3)
Vomiting	13 (2.0)	10 (1.5)	11 (1.7)	10 (1.5)
Headache	26 (4.0)	23 (3.5)	25 (3.8)	23 (3.5)
Diarrhea	8 (1.2)	19 (2.9)	8 (1.2)	19 (2.9)
Gamma-glutamyltransferase increased	13 (2.0)	12 (1.8)	7 (1.1)	5 (0.8)
Alanine aminotransferase increased	13 (2.0)	9 (1.4)	8 (1.2)	6 (0.9)
Aspartate aminotransferase increased	11 (1.7)	2 (0.3)	6 (0.9)	0
Pruritus	6 (0.9)	18 (2.8)	6 (0.9)	18 (2.8)
Rash	11 (1.7)	9 (1.4)	10 (1.5)	9 (1.4)
Pyrexia	8 (1.2)	11 (1.7)	8 (1.2)	7 (1.1)
Dizziness	8 (1.2)	6 (0.9)	8 (1.2)	6 (0.9)

Treatment-Emergent Adverse Events by Severity

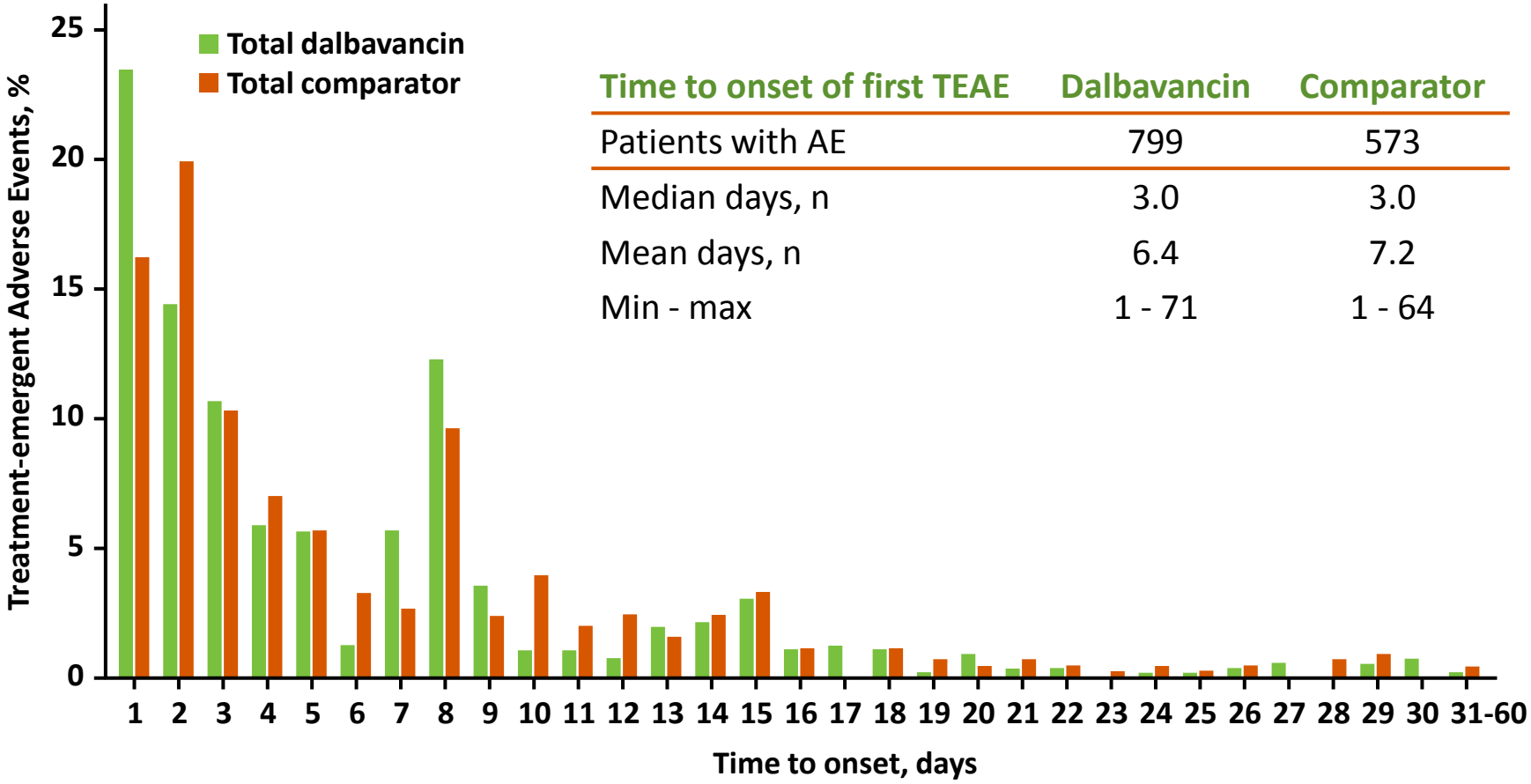
Phase 2/3

	Patients, n (%)	
	Dalbavancin N=1778	Comparator N=1224
≥1 AE	799 (44.9)	573 (46.8)
≥1 mild AE	648 (36.4)	447 (36.5)
≥1 moderate AE	340 (19.1)	275 (22.5)
≥1 severe AE	98 (5.5)	63 (5.1)

Day of Onset of Adverse Events

Phase 2/3

Late onset adverse events were seen at similar rates in patients treated with dalbavancin relative to those receiving comparator agents

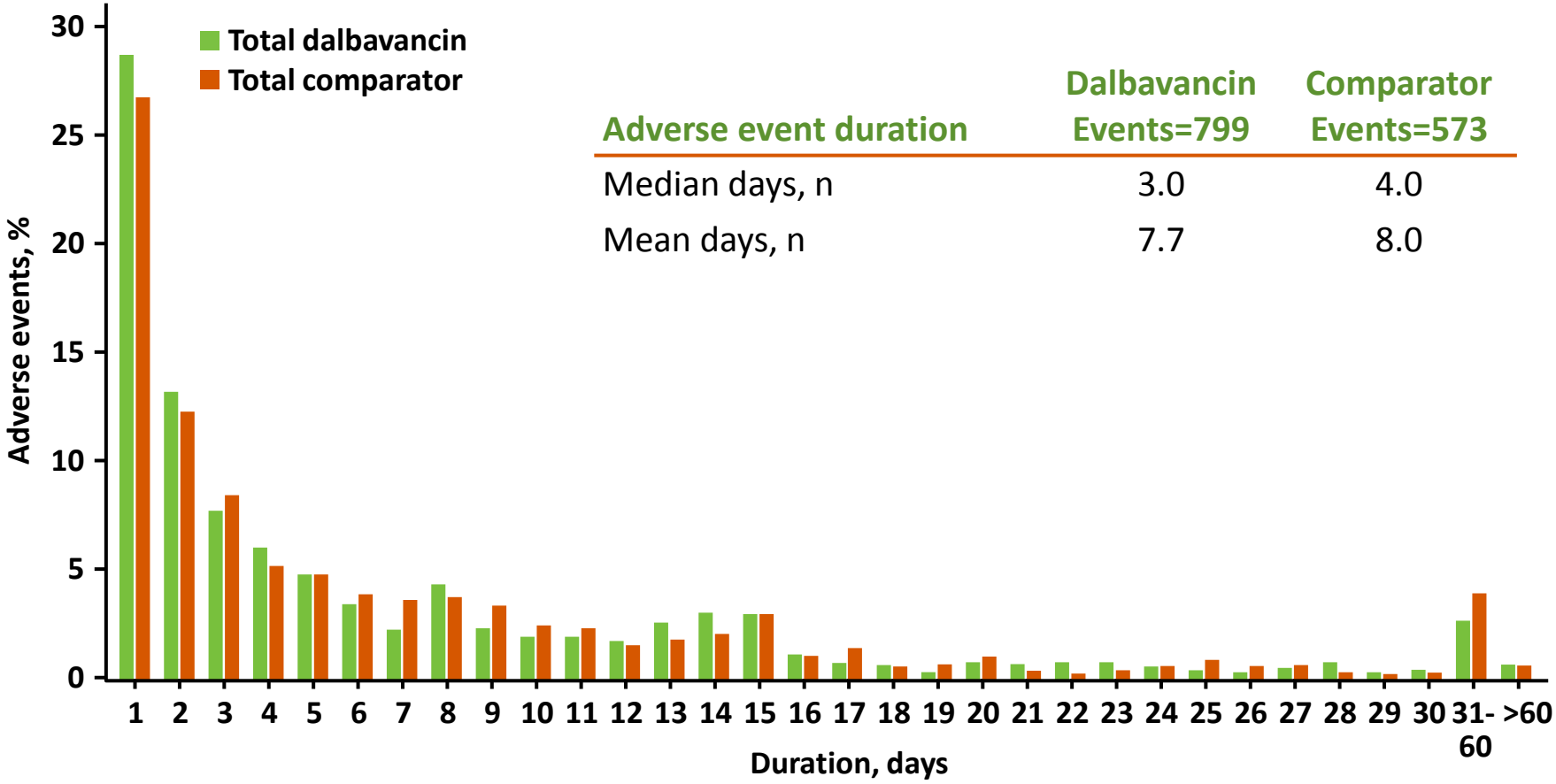


Time to onset of first TEAE	Dalbavancin	Comparator
Patients with AE	799	573
Median days, n	3.0	3.0
Mean days, n	6.4	7.2
Min - max	1 - 71	1 - 64

Duration of Adverse Events

Phase 2/3

The distribution of the duration of adverse events in patients receiving dalbavancin was similar to that on the comparator regimens



Adverse event duration	Dalbavancin Events=799	Comparator Events=573
Median days, n	3.0	4.0
Mean days, n	7.7	8.0

Overview of Treatment-Emergent Adverse Events by Special Population

Phase 2/3

Population	Patients with ≥1 TEAE, n/N (%)	
	Dalbavancin N=1778	Comparator N=1224
Age		
<65 years of age	641/1465 (43.8)	465/995 (46.7)
≥65 years of age	158/313 (50.5)	108/229 (47.2)
Gender		
Male	449/1066 (42.1)	308/711 (43.3)
Female	350/712 (49.2)	265/513 (51.7)
Race		
White	579/1388 (41.7)	448/1008 (44.4)
North America	437/782 (55.9)	310/503 (61.6)
Black or African American	90/143 (62.9)	58/88 (65.9)
North America	87/140 (62.1)	58/86 (67.4)
Asian	25/36 (69.4)	23/41 (56.1)
Other	105/211 (49.8)	44/87 (50.6)

Infusion-associated Adverse Events
Phase 2/3

	Dalbavancin N=1778	Comparator N=1224
Patients with infusion-associated AE, n (%)	40 (2.2)	38 (3.1)
Infusion-associated events, n	48	55
Events on day of active infusion, n	12	53

Renal-associated Adverse Events

Phase 2/3

	Patients, n (%)	
	Dalbavancin N=1778	Comparator N=1224
Treatment emergent adverse events		
Renal-associated AEs	33 (1.9)	24 (2.0)
Treatment-related renal-associated AEs	3 (0.2)	5 (0.4)
Serious adverse events		
All	3 (0.2)	6 (0.5)
Hydronephrosis	1 (0.1)	0
Nephrolithiasis	1 (0.1)	0
Acute renal failure	1 (0.1)	5 (0.4)
Nephropathy toxic	0	1 (0.1)
Treatment related	0	3 (0.2)
Acute renal failure	0	2 (0.2)
Nephropathy toxic	0	1 (0.1)

Clinical Laboratory Values
Creatinine
Phase 2/3 and DUR001-301/302

Phase 2/3: creatinine	Patients, n (%)			
	On treatment		End of treatment	
Creatinine (criteria)	Dalbavancin	Comparator	Dalbavancin	Comparator
≥1.5×ULN and ≥2-fold ↑	1 (0.1)	2 (0.2)	3 (0.2)	6 (0.6)
>ULN but normal at baseline	22 (1.8)	32 (3.8)	51 (3.6)	63 (6.6)
>ULN but high at baseline	64 (44.1)	59 (50.4)	69 (46.3)	63 (52.5)

DUR001-301/302: nephrotoxicity[a]	Patients, n/N (%)	
Population	Dalbavancin	Vancomycin/Linezolid
ITT	21/637 (3.3)	31/638 (4.9)
Population	**Dalbavancin**	**Vancomycin**
Dalbavancin vs ≥10 day vancomycin	21/637 (3.3)	5/54 (9.3)
IV (placebo or vancomycin) for ≥10 days	1/58 (1.7)	5/54 (9.3)

[a] **Nephrotoxicity: >50% or 0.5 mg/dL increase in creatinine from baseline.**

Hematologic Adverse Events
Blood and Lymphatic System Disorders
Phase 2/3

	Patients, n (%)	
	Dalbavancin N=1778	Comparator N=1224
Treatment-emergent adverse events		
Blood and lymphatic system disorders	72 (4.0)	48 (3.9)
Treatment-related blood and lymphatic system disorders	24 (1.3)	16 (1.3)
Serious adverse events		
All	6 (0.3)	2 (0.2)
Febrile neutropenia	2 (0.1)	0
Leukopenia	2 (0.1)	0
Anemia	1 (0.1)	0
Leukocytosis	1 (0.1)	0
Pancytopenia	0	1 (0.1)
Thrombocytopenia	0	1 (0.1)
Treatment related	1 (0.1)	2 (0.2)
Leukopenia	1 (0.1)	0
Pancytopenia	0	1 (0.1)
Thrombocytopenia	0	1 (0.1)

Clinical Laboratory Values
Hematology
Phase 2/3

Clinical laboratory parameter (potentially clinical significant criteria)	Patients, n (%)			
	On treatment		End of treatment	
	Dalbavancin	Comparator	Dalbavancin	Comparator
Hematocrit (≤0.8×LLN and ≥0.25-fold ↓)	5 (0.4)	6 (0.7)	5 (0.3)	4 (0.4)
Platelets (≤0.6×LLN and ≥0.4-fold ↓)	7 (0.6)	7 (0.8)	2 (0.1)	4 (0.4)
WBC (≤0.5×LLN and ≥0.75-fold ↓)	2 (0.2)	2 (0.2)	1 (0.1)	1 (0.1)

- No significant difference in laboratory safety assessments between dalbavancin and comparators

Hemorrhage: SMQ Assessment

- Relative risk of hemorrhage was not different in patients receiving dalbavancin relative to those receiving comparator agents

Population	Dalbavancin	Comparator	Relative risk (95% CI)
Phase 2/3 data	36 (2.0%)	19 (1.5%)	1.33 (0.76, 2.3)

- In FDA's focused review of DUR001-301 and 302, a subset of the total Phase 2/3 exposure, 13 events in 12 patients were noted in patients given dalbavancin compared to 3 in those receiving the comparator agent
- The events identified in patients receiving dalbavancin in DUR001-301/302 do not support a causal or complicating relationship:
  - 6/13 events occurred prior to the patient receiving dalbavancin
  - Remaining events had well described, plausible risk factors and no complications beyond the typical interventions required for patient management

SMQ Hemorrhage—Dalbavancin

Studies DUR001-301/302

Verbatim term	Description or history related to event	Timing
Chronic blood-loss anemia	No acute bleeding event; Fe deficient; anemic at baseline	Prior to dalba
Bleeding from operative wound	Traumatic injury with cellulitis drained after randomization but before dosing	Prior to dalba
Post-hemorrhagic anemia		Prior to dalba
Hematuria	Hx of hematuria ; baseline UTI + rbc; On platelet inhibitor	Prior to dalba
Melena (Black Blood in Stool)	Hct = 27 at baseline; alcoholic on NSAID with gastric erosions; 'old blood' noted 21 hours after first dose; no active bleeding on gastroscopy	Prior to dalba
Spontaneous hematoma in leg	Collection at site of infection was drained on Day 5	Ecchymosis at baseline
Upper GI Bleeding	Baseline anemia; ASA, NSAID, steroids; gastric ulcer	D6-28
GI bleed[a]	Renal failure; peptic ulcer	D8-13
Hematochezia	Drops of blood on stool; anal fissure on proctoscopy	D29-43
Petechiae bilateral lower extremities	Concurrent folliculitis with scabbing; ant bites	D8-15
Hematuria	Microscopic hematuria on colchicine	D2-15
Hematoma, lower arm venipuncture	Small hematoma; frail, elderly, low albumin	D17-24
Epistaxis	Coincident URI; lasted one hour; held nose	D5

[a] **Serious adverse event.**

SMQ Hemorrhage—Vancomycin
Studies DUR001-301/302

Verbatim term	Description or history related to event	Timing
Rectal hemorrhage	Platelet count 123k at baseline but normal subsequently	D29
Epistaxis	History of IVDU	D6-8
GI bleed[a]	On aspirin from Day 1-28	D28-29

[a] **Serious adverse event.**

Hepatic Adverse Events
Phase 2/3

	Patients, n (%)	
	Dalbavancin N=1778	Comparator N=1224
Treatment-emergent adverse events		
Hepatobiliary	19 (1.1)	9 (0.7)
Treatment related - hepatobiliary	6 (0.3)	1 (0.1)
Serious adverse events		
All	3 (0.2)	2 (0.2)
Biliary dyskinesia	1 (0.1)	0
Acute cholecystitis	1 (0.1)	1 (0.1)
Hepatic Lesion	1 (0.1)	0
Cholecystitis	0	1 (0.1)
Treatment related	0	0

Elevations in ALT at Follow-up
Unique Patients: Maximal Elevation
Phase 2/3 Compared with DUR001-301/302

Baseline ALT	Parameter (post-baseline)	Phase 2/3 Dalbavancin Total	Phase 2/3 Comparator Total	DUR001-301/302 Dalbavancin Total	DUR001-301/302 Comparator Total
All Patients	Total >ULN	417/1707 (24.4)	307/1186 (25.9)	157/638 (24.6)	151/635 (23.8)
	ALT >ULN - 3×ULN	373 (21.9)	276 (23.3)	135 (21.2)	136 (21.4)
	ALT >3 - 5×ULN	35 (2.1)	22 (1.9)	17 (2.6)	14 (2.2)
	ALT >5 - 10×ULN	5 (0.3)	7 (0.6)	2 (0.3)	1 (0.2)
	ALT >10xULN	4 (0.2)	2 (0.2)	3 (0.5)	0
Normal ALT	Total >ULN	218/1437 (15.2)	139/975 (14.3)	69/515 (13.4)	65/529 (12.3)
	ALT >ULN - 3×ULN	206 (14.3)	137 (14.1)	63 (12.2)	64 (12.1)
	ALT >3 - 5×ULN	7 (0.5)	1 (0.1)	3 (0.6)	1 (0.2)
	ALT >5 - 10×ULN	2 (0.1)	1 (0.1)	1 (0.2)	0
	ALT >10xULN	3 (0.2)	0	2 (0.4)	0
Elevated ALT	Total >ULN	173/237 (73.0)	155/197 (78.7)	82/102 (80.4)	82/103 (79.6)
	ALT >ULN - 3×ULN	143 (60.3)	127 (64.5)	67 (65.7)	68 (66.0)
	ALT >3- 5×ULN	26 (11.0)	20 (10.2)	13 (12.7)	13 (12.6)
	ALT >5 - 10×ULN	3 (1.3)	6 (3.1)	1 (1.0)	1 (1.0)
	ALT >10xULN	1 (0.4)	2 (1.0)	1 (1.0)	0

All patients = any ALT >ULN after baseline; Normal/Elevated ALT groups had both baseline and follow up ALT.

Elevations in ALT at Follow-up Category Above ULN

Phase 2/3 Compared with DUR001-301/302

Baseline ALT	Parameter (post-baseline)	Phase 2/3 Dalbavancin Total	Phase 2/3 Comparator Total	DUR001-301/302 Dalbavancin Total	DUR001-301/302 Comparator Total
All Patients	Total	1707	1186	638	635
	ALT >ULN	417 (24.4)	307 (25.9)	157 (24.6)	151 (23.8)
	ALT >3x	44 (2.6)	31 (2.6)	22 (3.4)	15 (2.4)
	ALT >5x	9 (0.5)	9 (0.8)	5 (0.8)	1 (0.2)
	ALT >10x	4 (0.2)	2 (0.2)	3 (0.5)	0
Normal ALT	Total	1437	975	515	529
	ALT >ULN	218 (15.2)	139 (14.3)	69 (13.4)	65 (12.3)
	ALT >3x	12 (0.8)	2 (0.2)	6 (1.2)	1 (0.2)
	ALT >5x	5 (0.3)	1 (0.1)	3 (0.6)	0
	ALT >10x	3 (0.2)	0	2 (0.4)	0
Elevated ALT	Total	237	197	102	103
	ALT >ULN	173 (73.0)	155 (78.7)	82 (80.4)	82 (79.6)
	ALT >3x	30 (12.7)	28 (14.2)	15 (14.7)	14 (13.6)
	ALT >5x	4 (1.7)	8 (4.1)	2 (2.0)	1 (1.0)
	ALT >10x	1 (0.4)	2 (1.0)	1 (1.0)	0

All patients = any ALT >ULN after baseline; Normal/Elevated ALT groups had both baseline and follow up ALT.

Normal ALT at Baseline
ALT >10×ULN at EOT
Phase 2/3

- 47 year old white female, history of chronic hepatitis C, BMI 31.2; received 2 doses of dalbavancin; Received metamizole and ketorolac on Day1 for pain relief
- **Acute epigastric pain** on Day 8**, Gallstones, CBD 6-7mm, echo-dense liver, enlarged spleen** noted on US/MRI; AE felt to be unlikely related to drug

Test	Baseline	Day 3	Day 8	Day 14	Day 17	Day 27	Normal range
ALT	19	22	219	622	251	41	0-45
AST	24	26	308	85	49	63	0-41
GGT	141	119	—	119	—	102	2-65
AP	121	120	—	210	227	126	35-104
Total bilirubin (Conj)	0.6	0.2	3.3 (2.1)	5.8 (5.0)	6.0 (3.5)	2.4 (1.1)	0.1-1.2

- **Confounding factors**
  - **Cholecystitis/choledocholithiasis** based on pain, gall stones/thickened GB wall ;
    - 28% of patients with choledocholithiasis in one study had ALT or AST levels >500 IU/L
  - **Hepatitis C**
  - **Metamizole** is associated with cholestatic hepatic hypersensitivity (and an ALT >500 IU/l)
  - **Ketorolac** is associated with abnormal serum aminotransferases; decreases arterial blood flow
- **Impression:** Episode of gallstone disease with cholestasis

Normal ALT at Baseline
ALT >10×ULN at EOT
Phase 2/3

- 48 year old white male, IV drug abuse, hepatitis C, and ongoing heroin use
- **Serum toxicology** exam performed on a baseline documented presence of both **morphine and methadone;** Patient admitted to **drinking '3 beers' and injecting IV heroin** on day of EOT visit

Test	Baseline	Day 3	Day 14/15	Day 20	Day 70	Normal range
ALT	29	28	589	127	43	0-45
AST	21	23	248	66	46	0-41
GGT	162	121	566	417	255	2-65
AP	135	106	274	182	113	40-129
Total bilirubin	0.5	0.3	0.6	0.3	0.3	0.1-1.2

- **Confounding factors**
  - Hepatitis C
  - Injection drug use
  - Alcohol abuse

- **Impression:** The increases in aminotransferases in a patient with underlying chronic hepatitis C are secondary to recent injection drug and alcohol use.

Elevated ALT at Baseline ALT >10×ULN at EOT

Phase 2/3

- 26-year-old White male, history of IV drug abuse and alcoholic hepatitis; received 2 doses of dalbavancin; conmeds included tramadol, codeine and oxycodone from Days 1-4

Test	Baseline	Day 3	Day 15	Day 27	Day 61	Normal range
ALT	55	115	503	221	145	0 - 45
AST	57	99	200	87	69	0 - 41
GGT	33	41	123	NA	NA	2 - 65
AP	91	94	139	146	111	40 - 129
Total bilirubin	0.2	0.3	0.2	0.5	0.4	0.1 - 1.2

- **Confounding Factors:**
  - IV drug abuse
  - Use of multiple opioids
  - History of alcoholic hepatitis
- **Impression**: Increases in aminotransferases in subject with history of IVDU and alcoholic hepatitis likely due to co-administration of multiple opiates.

Normal ALT at Baseline
ALT >10×ULN at TOC
Phase 2/3

- 33 year old white male, no significant past medical history
- Patient admitted to acute increase in alcohol consumption during his vacation from Day 23 to Day 25; alcoholic hepatitis reported as an adverse event

Test	Baseline	Day 8	Day 27	Day 35	Day 357	Normal range
ALT	14	16	953	317	41	0 - 47
AST	23	25	716	83	25	0 - 37
GGT	18	19	148	96	—	0 - 51
AP	81	100	131	99	—	40 - 135
Total bilirubin	0.6	0.4	0.5	0.6	—	0 - 1.11

- **Confounding factors**
  - Alcohol abuse

- **Impression**: Increases in aminotransferases are a consequence of recent binge alcohol intake.

Elevated ALT at Baseline
ALT >10×ULN at EOT (Comparator)
Phase 2/3

- 55 year old white male with hepatitis B who received 28 doses of vancomycin. He also received numerous concomitant medications including acetaminophen (up to 28 grams), morphine, clonazepam, metoclopramide, and ketorolac.

Test	Baseline	Day 2	Day 4	Day 9	Day 16	Day 35	ULN
ALT	174	245	207	473	592	34	38
AST	135	184	110	354	158	19	40
GGT	445	453	359	—	293	99	50
AP	165	169	189	365	425	282	92
Total bilirubin	3.0	2.9	3.7	2.3	1.6	0.8	1.2

- **Confounding factors**
  - Hepatitis B
  - Multiple concomitant medications
- **Impression:** Increase in serum aminotransferases in patient with abnormal liver function tests at baseline likely due to underlying hepatitis B and multiple concomitant medications.

Elevated ALT at Baseline
ALT >10×ULN at Follow-up (Comparator)
Phase 2/3

- 40 year old white male, history of elevated GGT and ALT; received 6 days of vancomycin followed by oral linezolid for 9 days; Received numerous concomitant medications including oxycodone/acetaminophen from day -2 to day 6 (up to 7.8 grams of acetaminophen); pethidine (Demerol) from day 1 to 6, and ketorolac.

Test	Baseline	Day 5	Day 16	Normal range
ALT	79	472	125	0-39
AST	33	223	49	0-41
GGT	177	187	153	0-36
AP	93	95	85	—
Total bilirubin	0.6	0.6	0.7	0-1.1

- **Confounding factors**
  - History of elevated GGT and ALT at baseline
  - Multiple concomitant medications
- **Impression:** Elevated aminotransferases in patient with baseline liver function abnormalities likely due to co-administration of multiple medications including acetaminophen and narcotics.

Conclusion
Serum Aminotransferases

- Patients in clinical trials of serious skin infections have been shown to develop serum aminotransferase elevations while on therapy, including 24.4% patients treated with dalbavancin and 25.9% on the comparator agents.
- 4/1707 (0.2%) of patients treated with dalbavancin and 2/1186 (0.2%) treated with the comparator developed >10xULN elevations in ALT on therapy
  - These aminotransferases either completely resolved or were returning to normal while still on study drug
  - All of these patients had alternative explanations other than study drug for these elevated ALT assessments

Well-Characterized and Consistent Safety Profile Across Multiple Large Clinical Studies

- Types and severity of AEs identified those typically seen in patients with SSSI and generally comparable between treatment arms
  - Treatment-related AEs, all-causality AEs, and SAEs experienced at similar rate in dalbavancin and comparator groups
- Most AEs were of mild intensity and resolved spontaneously
  - Duration of adverse events not longer than comparator
- Extensive evaluation of special populations of interest did not reveal a specific population at higher risk for an unfavorable safety profile
- Maximally tolerated dose of dalbavancin has not been established
  - Treatment of overdose with dalbavancin should consist of observation and general supportive measures

Summary and Conclusion

Dalbavancin Demonstrates a Favorable Benefit:Risk Profile for Patients With ABSSSI

- Consistently effective in patients with ABSSSI regardless of clinical variables and endpoints assessed in a patient population enhanced for severity of illness
  - Only two doses required
  - Bactericidal levels throughout the treatment period
  - Activity against MRSA and low potential for resistance development
- Well-characterized safety profile across multiple large trials
  - No need for indwelling IV catheters, including PICC lines
  - Weekly IV dosing regimen avoids daily oral antibiotics
  - No weight based dosing
  - No drug interactions
  - No need for therapeutic drug monitoring
  - No effect on bone marrow function
  - No teratogenicity

Dalbavancin for the Treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

United States Food and Drug Administration

Anti-infective Drugs Advisory Committee

March 31, 2014

DURATA THERAPEUTICS®

Supportive Slides

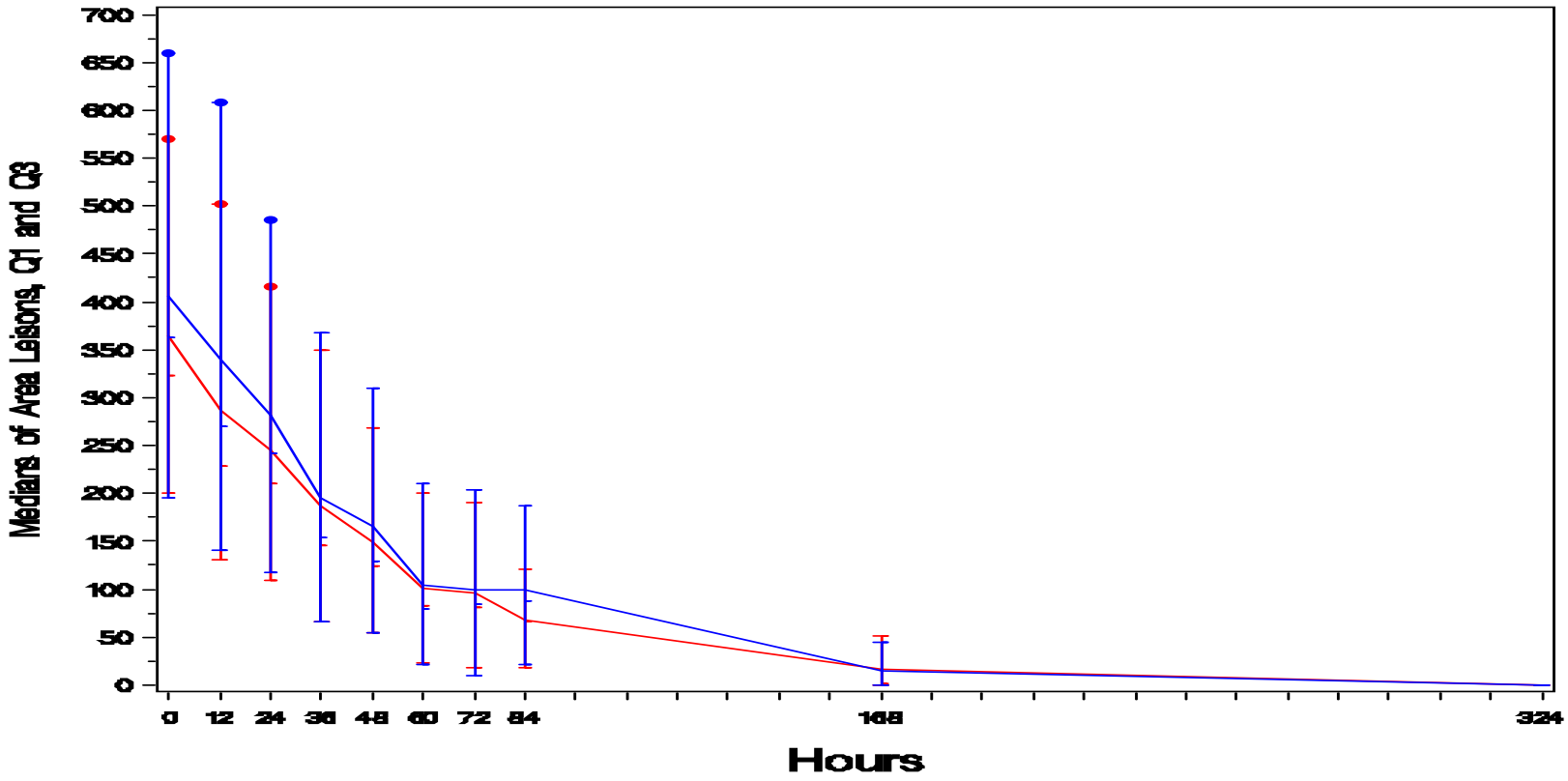
Median Lesion Size with IQR

Baseline and Early Time point

DUR001-301/302

	Treatments Combined	Dalbavancin	Vancomycin / Linezolid
Baseline			
Quartile 3 (75%)	617	576.25	675.10
Median (50%)	341.2	324.0	366.8
Quartile 1 (25%)	200	201.45	198.65
48-72 hours			
Quartile 3 (75%)	182	165.65	195.0
Median (50%)	72	74.15	71.3
Quartile 1 (25%)	14.8	15.3	13.5

Medians Area of Lesions
ITT Population
Studies DUR001-301/302



Quartiles, over time

Duration of Rash[a]

Phase 2/3 Safety Population

Statistics	Dalbavancin N=1778	Comparators N=1224
N (%)	53 (3.0)	22 (1.8)
Mean	5.9	10.5
SD	4.21	10.13
Median	6	6.5
Min - max	1 - 19	1 - 39

[a] Includes generalized rash, pruritic rash, papular rash, macular rash, erythematous rash, pustular rash and maculopapular rash.

Vancomycin Outcomes by Vancomycin Serum Level or Dosing Regimen

DUR001-301/302

Efficacy outcomes	Patients, n/N (%) Vancomycin level <10 µg/mL	Vancomycin level ≥10 µg/mL
48-72 hour outcomes		
Success	79/95 (83.2)	78/94 (83.0)
Difference (95% CI)	0.2 (–10.7, 11.1)	
Clinical success at EOT		
Success	83/95 (87.4)	82/94 (87.2)
Difference (95% CI)	0.2 (–9.7, 10.0)	

Efficacy outcomes	Patients, n/N (%) Fixed-dose regimen	Weight-based regimen
48-72 hour outcomes		
Success	349/441 (79.1)	172/210 (81.9)
Difference (95% CI)	–2.8 (–9.0, 4.0)	
Clinical success at EOT		
Success	383/441 (86.8)	179/210 (85.2)
Difference (95% CI)	1.6 (–3.9, 7.8)	

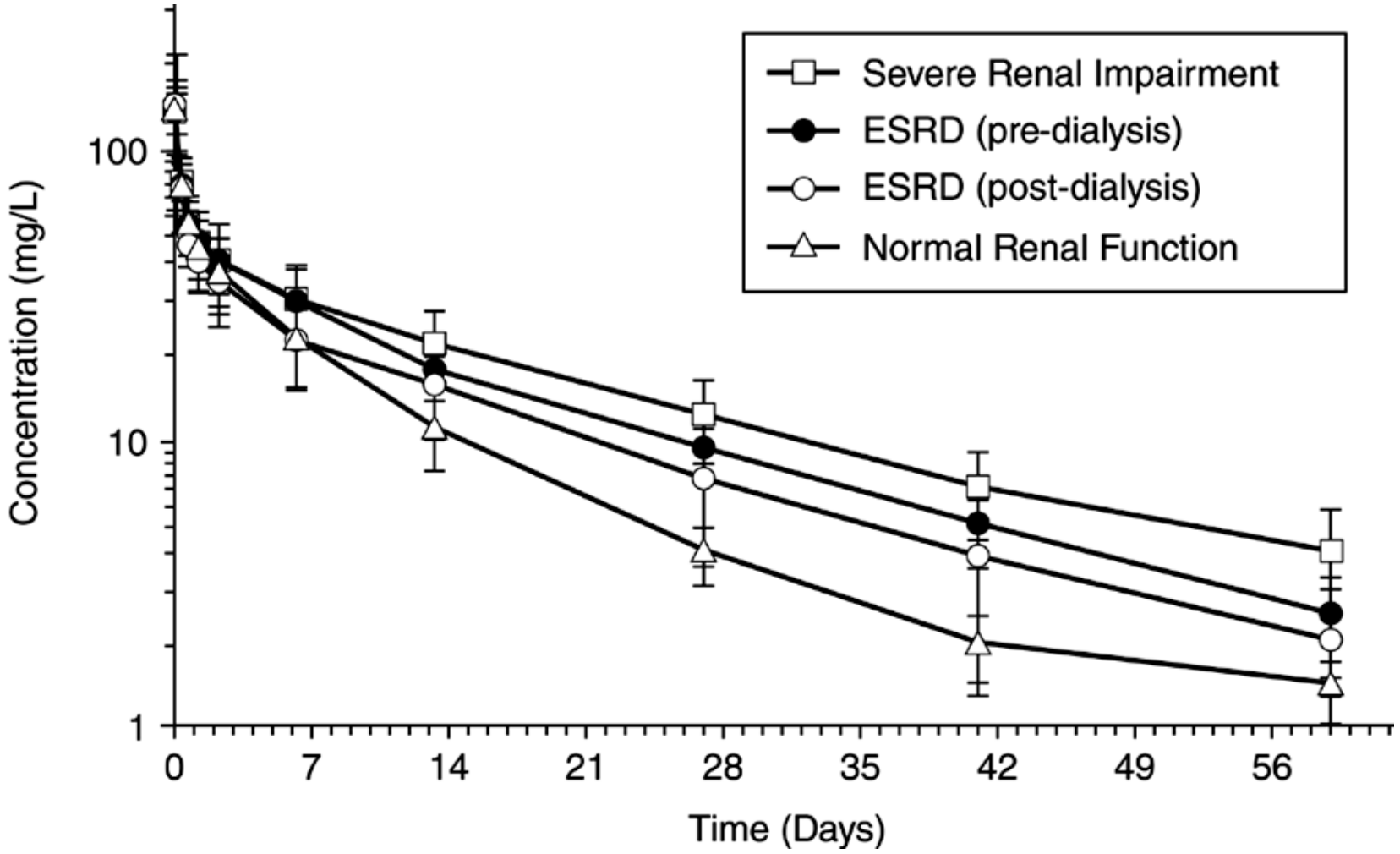
Clinical Response at 48-72 hr
BMI
Studies DUR001-301/302—ITT Population

	Patients, n/N (%)	
BMI category, kg/m²	Dalbavancin N=659	Vancomycin/ Linezolid N=653
<25	144/182 (79.1)	166/212 (78.3)
25 - <30	195/239 (81.6)	164/199 (82.4)
≥30	186/231 (80.5)	190/240 (79.2)

Covariate Analysis	Dalbavancin and association with Primary Endpoint Odds Ratio (95%CI)		
Category	301	302	301 and 302 Combined
BMI - ≥, < 25 kg/m²	0.92 (0.56, 1.51)	1.28 (0.89, 1.85)	0.88 (0.66, 1.19)
BMI - continuous	1.00 (0.98, 1.03)	0.99 (0.97, 1.02)	1.00 (0.98, 1.02)

Dalbavancin Plasma Concentration vs Time Profiles Following a 1000-mg Dose

Renal Impairment



Validation of Observer Variability in Lesion Measurement

DUR000-201

- Purpose: Assess variability in intra-and inter-observer measurements
- Methods: Ruler measurements of infection sites determined twice by first observer for assessment of intra-observer variability, then once by one to two other observers
  - Intraclass correlation coefficient (ICC) and coefficient of variation (COV) determined with 95% confidence intervals (CI). Bland-Altman plots of ruler vs other measurement techniques were created

	n	Mean (SD)	ICC (95% CI)	COV (95% CI)
Intra-observer				
Measurement 1	39	524.99 (543.038)	0.999 (0.998, 1.000)	3.08 (2.89, 3.27)
Measurement 2	39	526.13 (545.783)		
Inter-observer				
Observer 1	39	524.99 (543.038)	0.990 (0.981, 0.995)	10.38 (9.70, 11.06)
Observer 2	39	519.58 (543.879)		